Review Article

Androgen deprivation therapy and risk of cognitive dysfunction in men with prostate cancer: is there a possible link?

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ABSTRACT

The expansion of the indication to use androgen deprivation therapy (ADT) to treat patients with advanced or metastatic prostate cancer has dramatically increased over the recent decades, resulting in the progress of patients' survival. However, chronic health implications can become more apparent as the number of long-term cancer survivors is expected to be increased along with the adverse effect of ADT. In particular, interest in investigating ADT, especially luteinizing hormone-releasing hormone (LHRH) agonist association with cognitive dysfunction has been growing. Previous studies in animals and humans suggest that the level of androgen decreases with age and that cognitive decline occurs with decreases in androgen. Correspondingly, some of the extensive studies using common neurocognitive tests have shown that LHRH agonists may affect specific domains of cognitive function (e.g., visuospatial abilities and executive function). However, the results from these studies have not consistently demonstrated the association because of its intrinsic limitations. Large-scale studies based on electronic databases have also failed to show consistent results to make decisive conclusions because of its heterogeneity, complexity of covariates, and possible risk of biases. Thus, this review article summarizes key findings and discusses the results of several studies investigating the ADT association with cognitive dysfunction and risk of dementia from various perspectives.

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1. Introduction

Widespread use of prostate-specific antigen test and subsequent biopsy have been determined to significantly contribute to the increased diagnosis of prostate cancer (PCa) over the last two decades.[1,2] Furthermore, randomized evidence supports the use of androgen deprivation therapy (ADT) in combination with external beam radiation therapy for locoregional disease with high-risk features although ADT has been widely used to treat metastatic PCa.[3,4] Correspondingly, the use of ADT has dramatically increased, and about 50% of patients are treated with ADT at some stage of PCa diagnosis.[5–7]

However, ADT may cause several adverse health events (e.g., hot flashes, osteoporosis, anemia, gynecomastia, erectile dysfunction, obesity, muscle atrophy, loss of bone mineral density, and mood disorders)[8] that are related to low male androgens because of its testosterone-suppressing effect. Moreover, ADT is also known for its adverse effect such as increased risk of metabolic syndrome and cardiovascular diseases.[9] In particular, ADT has been known to negatively affect cognitive function, which may, in turn, affect a patient's ability to make informed treatment decisions, occupational or intellectual pursuits, and overall quality of life. As aforementioned, broadening of indications for ADT use and early use of ADT in PCa patients means that they will, on average, be treated with ADT for a longer time over the disease course. As the number of long-term cancer survivors is expected to increase, the chronic health implications of ADT including cognitive dysfunction will become increasingly important.

No definitive conclusions have been reached on the association of ADT with cognitive dysfunction and risk of dementia although extensive research has been focused on this field. Several previous studies have shown that ADT may worsen performance in certain cognitive domains,[10,11] whereas others showed no association between ADT and neuropsychological tests.[12,13] More recently, reports

on the association of ADT with increased risk of Alzheimer's disease (AD) and other types of dementia based on large electronic databases have also demonstrated contradictory results.[14-23] Apart from these controversies, the prevalence of dementia in South Korea among elderly men (≥65 years) was recorded to be as high as 9.2%,[24] which indicates that exploring the correlation between ADT and risk of dementia is based on a population already at increased risk and therefore requires careful considerations. In this current review, we discuss the general impact of androgen level on cognitive function and further examine the results from previous studies that have investigated the association of ADT with cognitive dysfunction or risk of dementia in PCa patients.

2. Possible mechanisms of testosterone on cognition

2.1. ADT, cardiovascular diseases, and its association with dementia

AD and vascular dementia have been considered completely different and distinct diseases in the past. However, it is now generally thought that both can be accompanied frequently. This means that these two types of dementia share several common risk factors and pathologic features with atherosclerosis.[25] Moreover, traditionally accepted cardiovascular risk factors (e.g., hypertension, dyslipidemia, and diabetes) appear to be associated with an increased risk of not only vascular dementia, but also AD. Numerous observational studies have shown the correlation between hypertension and diabetes with dementia; hypertension in mid-age have consistently increased the risk of all-cause dementia including AD,[26,27] and patients with diabetes were found to have a doubled risk of developing vascular dementia[28,29] as well as a relatively higher risk of AD compared with those without diabetes.[30] These cardiovascular diseases can cause oxidative cell damage, inflammation, and insulin resistance, resulting in blood vessel dysfunction and stroke-like damage, leading to dementia.[31]

The association between cardiovascular diseases and the risk for dementia can lead to controversy over whether ADT directly increases the risk of dementia. Because ADT may also be associated with cardiovascular disease, ADT may not be directly related to the risk of dementia, but it can indirectly increase the risk of dementia by increasing the risk of cardiovascular diseases. These cardiovascular diseases are also linked to testosterone, which further complicates conclusions.

2.2. Age-related changes in androgen levels in the brain tissue

Men often experience a significant decline in circulating testosterone levels through the aging process.[32] However, the difference between the concentrations of testosterone at the serum and tissue level can often be found because factors such as sex hormone-binding globulin (SHBG) and steroid-converting enzymes may create such difference.[33,34] Therefore, the testosterone level in a specific tissue is expected to more accurately reflect the actual measure of bioavailable testosterone. An animal study examining the brain levels of sex steroids in male rats has explored the significant reduction in brain levels of the potent androgen dihydrotestosterone (DHT) with increasing age.[35] The authors of this study have also reviewed the male postmortem brain tissues neuropathologically in their follow-up research, wherein they found that normal aging was associated with significant decreases in both testosterone and DHT.[36] In particular, brain testosterone levels were found to be lower in cases with mild neuropathological changes or AD than normal cases in men aged 60-79 years.[36]

2.3. The role of testosterone in the brain

Previous extensive studies found that changes in the sex steroid levels can have a structural and functional effect on the brain. Huppenbauer et al. noted that approximately 20% of neurons were rescued by applying testosterone or estrogens to transected facial nerve neurons using facial motor neurons from hamsters.[37] In an experiment using male mice that had undergone gonadectomy, testosterone and DHT can also lower β-amyloid accumulation in the hippocampus, which may probably result in reducing the risk of dementia in humans.[38] Another similar research observed that synaptic density of hippocampus CA1 region in rats decreased with castration and reversed by testosterone or DHT administration.[39] Moreover, testosterone supplementation was also seen to enhance cerebral perfusion in the superior frontal gyrus and cingulated gyrus of hypogonadal men, which was assessed by single-photon emission computed tomography.[40] Conversely, testosterone suppression by androgen blockade resulted in decreased cerebral glucose metabolism or decreased gray matter volume in the cerebral cortex, which was assessed by fluorine-18 fluorodeoxyglucose positron emission tomography and high-resolution magnetic resonance imaging, respectively.[41,42] Testosterone also exerts its effect on cognition by modulating G-protein−coupled receptor, neurotransmitters, and cholinergic activity (Fig. 1).[43-45]

To summarize, testosterone may have a certain role in neuronal regeneration and testosterone brain level can be possibly related to brain function. Furthermore, testosterone may exert its effect on cognition by modulating the hippocampus, which is supported by many animal and human studies.[46] However, testosterone has been suggested to indirectly induce cognitive dysfunction through other factors, such as cardiovascular illnesses.

3. Serum testosterone levels and cognitive function

3.1. Positive association between testosterone levels and cognitive function

The production of testosterone in men declines slowly and consistently after reaching the age of 30 years. Moreover, the rate of hypogonadism in men in their 50s, 60s, 70s, and 80s were 9%, 34%, 68%, and 91%, respectively.[47] The findings from studies of elderly or hypogonadal men generally indicate that serum testosterone level is associated with cognitive performance in men although they are not entirely consistent.[48,49] Especially, men with high serum levels of bioavailable testosterone, not total testosterone, were determined to have better cognitive scores such as in the Mini-Mental State Examinations in a cross-sectional study.[50] In the same context, the serum level of SHBG was negatively associated with cognitive scores in this observation.[50] Thus, supplementing testosterone has also been proven to be associated with beneficial changes in cognitive function, particularly verbal and spatial memory in several randomized controlled trials.[51-53]

3.2. Controversial results on the association between androgen and cognitive function

In contrast to the aforementioned studies, a few cross-sectional analyses showed that various sex steroids such as testosterone, estradiol, dehydroepiandrosterone (DHEA), or dehydroepiandrosterone sulfate (DHEAS) were not related to cognitive decline.[54,55] Furthermore, a cross-sectional study of 450 men even reported that men with lower free testosterone performed better on spatial visualization tasks compared with those with higher testosterone, showing fairly opposite results to previous studies.[56] More complex results have been reported by Geerlings et al. by examining the
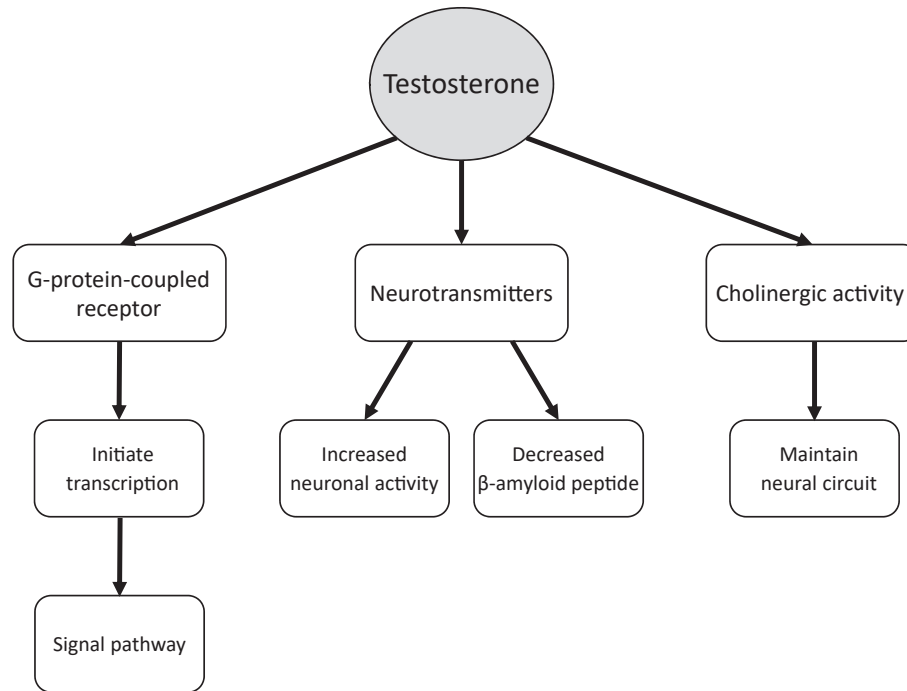
Fig. 1. The potential mechanism of testosterone affecting cognition.

correlation between sex hormones with cognitive decline and future dementia in a large longitudinal study of 2,974 men. They found intriguing results that bioavailable testosterone was not associated with the risk of dementia, whereas higher bioavailable estradiol levels predicted increased incidence of AD.[57]

To summarize up-to-date findings on the association between serum testosterone levels and cognitive function, a large number of previous studies suggest that the depletion of testosterone may negatively impact the areas of working memory, verbal memory, and visual-spatial ability. However, some contradictory results exist on this issue, and the difference in the results can be even more significant when different sex steroids such as estrogen, DHEA, and DHEAS are taken into consideration. It is presumed that the difference in the results from the previous aforementioned studies is probably due to its potential intrinsic limitations. First, no uniform methods for the measurement of hormones exist (e.g., radioimmunoassays, mass spectrometry, and so on). Second, adjustment errors for other covariates including education, alcohol, depression, or other medical comorbidities may exist.[58]

4. Dementia and ADT in men with prostate cancer

4.1. The impact of serum testosterone reduction on the cognitive function in patients undergoing ADT.

Since the beginning of the 21st century, numerous small-scale studies have steadily suggested that ADT influences cognitive function in patients with PCa. An earlier study with 50 men undergoing luteinizing hormone-releasing hormone (LHRH) agonist treatment and 15 controls reported that patients with LHRH agonists, especially goserelin, showed significant decreases in verbal and visual memory when compared to the control group. Of the 50 men on LHRH agonist treatment, 24 men demonstrated a reliable decline in cognitive tasks, whereas the control group showed no decline on any of the tasks including memory, attention, and executive functions.[59] As per the results of an analysis of 26 patients whose testosterone

reached castrate levels after 6 months of LHRH agonist administration, the decline in serum testosterone coincided with a decline in visuomotor processing (digit symbol) and working memory speed (subtraction).[11] Interestingly, when the LHRH agonist was ceased after 9 months of treatment, patients' decreased visuospatial ability within 9 months of LHRH agonist administration returned to normal levels after 3 months without LHRH agonists, which further implies the effect of ADT on cognitive function.[10]

On the contrary, a result from a longitudinal study investigating 37 PCa patients receiving a 36-week course of LHRH agonists was quite the opposite.[60] This study assessed cognition eight times over 1 year with tests of verbal memory, visual memory, and visuospatial ability. At the end of the 36-week LHRH agonist treatment course, the researchers observed an increased performance on a test of verbal and visual memory, which suggests that treatment with LHRH agonists may have a positive impact on cognitive function. This contradictory result, however, may be criticized because the repetition of neuropsychological tests may lead to the patient's improvement over time with practice: improved cognition ability may be caused by the artifacts of practice effects. Nevertheless, a more recent cross-sectional study of 198 men revealed only a weak association of total testosterone with working memory, and neither total testosterone nor estradiol was related to other cognitive domains such as verbal fluency, visuospatial abilities, verbal memory, and visual memory, supporting the contradictory results.[61] It is presumed that one of the important reasons for the aforementioned inconsistent results is probably because different definition and measurement tools to assess cognitive dysfunction were used for each study as shown in Table 1. Thus, further investigations are warranted to confirm the actual effect of suppressing testosterone by ADT on cognitive function changes.

4.2. The role of estrogen

Several previous studies have also suggested that estradiol changes during ADT affect cognition in men with PCa. A study in

Table 1
Representative prospective studies on the association between ADT and cognitive dysfunction.

Year	Author	Study design		No. of patients			ADT duration	Cognitive assessment		Cognitive function affected
		Randomization	Disease state	ADT	Control			Cognitive parameters	Measurement tools	
					Prostate cancer	Healthy				
2002	Green[59]	Yes	Advanced	50	15	None	6 mo	Memory, attention, executive function	WMS-R, AVLT, WAIS-R, TMT, COWA	All affected
2004	Almeida[60]	No	Not specified	37	None	None	13.5 mo	Depression, anxiety, verbal memory, general mental health	WMS-III, CAMCOG, BDI, BAI	Verbal memory
2005	Jenkins[64]	No	Localized	32	None	18	9 mo	Intelligence, verbal ability, verbal memory, visual memory, visual-spatial memory, processing speed	FSIQ, NART, PVFT, RAVLT, CFT, CMRT, KACAB	Spatial memory & ability
2010	Alibhai[13]	No	Not specified	77	82	82	12 mo	Processing speed, verbal fluency, visuospatial ability, verbal memory, executive function	MMSE, NAART, TMT	Not affected
2015	Gonzalez[71]	No	Asymptomatic	58	84	88	12 mo	Verbal memory, visual memory, attention, executive function	HVLT-R, WMS-III, BVMT-R, COWA	Attention, executive function
2015	Yang[72]	No	Nonmetastatic	43	35	40	6 mo	Memory, short-term memory, executive function, processing speed	MoCA test, WAIS, TMT	Prospective memory
2017	Gunslusoy[65]	Yes	Locally advanced or metastatic	78	78	None	12 mo	Attention & concentration, executive function, memory, language, orientation, abstract thinking	MoCA test, FAB test	Language ability, short-term memory, mental flexibility, inhibitory control
2017	Alibhai[73]	No	Nonmetastatic	77	82	82	36 mo	Immediate span of attention, processing speed, verbal fluency, visuospatial ability, verbal learning & memory, visual learning & memory, executive function	TMT, COWA, card rotations, CVL test, BVM test	Not affected

ADT, androgen deprivation therapy; AVLT, Auditory Verbal Learning Test; BAI, Beck Anxiety Inventory; BDI, Beck Depression Inventory; BVM, Brief Visual Memory; BVMT-R, Brief Visuospatial Memory Test−Revised; CAMCOG, Cambridge Examination for Mental Disorders of the Elderly; CFT, Complex Figure Task; CMRT, Computerized Mental Rotation Task; COWA, Controlled Oral Word Association; CVA, California Verbal Learning; FAB, Frontal Assessment Battery; FSIQ, Full Scale Intelligence Quotient; HVLT-R, Hopkins Verbal Learning Test−Revised; KACAB, Kendrick Assessment of Cognitive Aging Battery; MMSE, Folstein Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NAART, North American Adult Reading Test; NART, National Adult Reading Test; PVFT, Phonemic Verbal Fluency Task; RAVLT, Rey Auditory-Verbal Test; TMT, Trail Making Test; WAIS-R, Wechsler Adult Intelligence Scale−Revised; WMS-R, Wechsler Memory Scale−Revised.

which 23 men with PCa were prospectively enrolled investigated the association between the decline of estradiol and cognitive performance.[62] Among various cognitive domains, visual memory of figures and recognition speed of numbers were impaired, whereas verbal fluency was improved with the decline of estradiol during ADT. Beer et al. specifically tested the effect of estradiol supplementation in patients with PCa undergoing ADT.[63] The researchers compared three groups: 18 patients with castration-resistant PCa undergoing ADT with estradiol administration, 18 age-matched patients with PCa undergoing continuous ADT, and 17 community-dwelling healthy men. Indeed, worse verbal memory and slower processing speed were noted in patients with ADT compared with healthy controls. However, no difference was noted in working memory tasks. Verbal memory performance improved with estradiol supplement, but it did not change in PCa patients without estradiol therapy and control group in repeated-measures analyses. Therefore, previous studies have suggested that estrogen in men with PCa receiving ADT plays a positive role in cognitive function.

The aforementioned studies focusing on the role of sex hormones such as testosterone or estrogen on cognition in patients with PCa are mostly cross-sectional or longitudinal studies, and based on a relatively small number of patients. However, large-scale studies using registered, cohort database that examined the relationship between ADT and cognitive function or the risk of dementia were announced intensively thereafter (Table 2), with the development of techniques for manipulation of a great amount of registry data.

4.3. ADT increases the risk of cognitive dysfunction or dementia

The first report from a large cohort analysis using novel informatics technique based on the electronic medical records was released in 2016 by Nead et al.[14] The authors have extracted diagnosis codes, medication lists, and mentioned drugs and diseases from clinical notes from the registry data in a retrospective cohort of patients and explored the association of ADT with LHRH agonists in the treatment of PCa with subsequent risk of AD in 16,888 patients (2,397 with ADT). A significant association of LHRH agonist use and increased AD risk with a hazard ratio (HR) of 1.88 and the correlation between the duration of LHRH agonist use with increased risk of AD were found. A similar result was reported in the succeeding protocol using a subcohort of 9,272 men (1,826 with ADT), extending to all types of dementia, which showed an even greater HR of 2.17 in patients undergoing ADT with LHRH

agonists.[23] One of the most recent large retrospective cohort studies using TRICARE Military Database investigated the effect of ADT, particularly on the risk of depression along with those of dementia in 9,117 men (40–64 years old) diagnosed with localized PCa.[20] In this study, patients with ADT were determined to have a significantly higher risk of depression (HR, 2.07) and dementia (HR, 1.70). A dose–response relationship was noted between outcome and ADT duration. Another most recent large population-based study using the Surveillance, Epidemiology, and End Results database including 154,089 PCa patients revealed that both AD (HR, 1.140) and dementia (HR, 1.20) were significantly associated with ADT.[16] This study has its advantages over previous studies in that it included additional clinical variables, for example, tumor grade and being able to adjust for them. In addition, it has the longest reported mean follow-up of 8.3 years. Apart from studies using informatics approach evaluating registry databases, a few prospective studies found the association of impaired cognitive performance with ADT in PCa patients, especially in certain domains such as language ability, short-term memory, mental flexibility, and inhibitory control.[60,64,65]

4.4. No increased risk of impaired cognition or dementia in patients receiving ADT

In contrast, research from the United Kingdom using the national Clinical Practice Research Datalink tested the effect of ADT on all incident events of dementia, including AD in 15,310 versus 15,593 PCa patients with or without ADT, respectively. In this population-based study, either type or duration of ADT use was not associated with the risk of dementia during a mean follow-up of 4.3 years.[17] A few reports from the Asian series have also raised skeptical questions on the correlation between cognitive function and ADT.[18,21,22] Although LHRH agonist use was found to be associated with dementia in univariable analysis, the association was deemed not significant in the multivariable analysis adjusting covariables in a Korean study using data from the National Health Insurance Service (NHIS), which investigated the effect of ADT with LHRH agonist on both dementia and Parkinson's disease in 7,324 patients with PCa (3,201 LHRH agonist users).[18] The largest population-based cohort study to date with a mean follow-up of 5.5 years examining 1.2 million fee-for-service Medicare beneficiaries with PCa (35% received ADT) also observed no significant ADT effect on dementia risk. Although unadjusted rates of dementia were higher among ADT users (38.5 and 32.9 per 1,000 person-years in ADT users and nonusers, respectively), patients

Table 2
Observational studies examining the association between androgen deprivation therapy and cognitive function using large electronic registry database.

Year	Author	Study characteristics			Patients' demographics				Type of cognitive dysfunction	Association
		Country of origin	Period (y)	Mean follow-up (y)	Total no. (%)		Age at enrollment Mean ± SD (y)			
					ADT group	Control	ADT group	Control		
2016	Nead[14]	USA	1994–2013	2.7[a]	2,397 (16.7)	11,985 (83.3)	70.9 ± 10.8	70.9 ± 12.6	Alzheimer's disease	Positive
2016	Chung[21]	Taiwan	2001–2008	5.0	768 (57.5)	567 (42.5)	74.2 ± 8.0	69.5 ± 10.2	Alzheimer's disease	Negative
2017	Baik[15]	USA	2001–2014	5.5	440,129 (35.5)	798,750 (64.5)	76.7 ± 6.4	74.6 ± 6.6	All dementia	Negative
2017	Nead[23]	USA	1994–2013	3.4	1,826 (19.7)	7,446 (80.3)	69.9 ± 11.0	66.2 ± 10.8	All dementia	Positive
2017	Khosrow-Khavar[17]	UK	1988–2015	4.3	15,310 (49.5)	15,593 (50.5)	72.8 ± 8.3	68.7 ± 9.0	All dementia	Negative
2017	Kao[22]	Taiwan	2001–2008	5.0	755 (57.5)	559 (42.5)	74.2 ± 7.9	69.3 ± 10.1	All dementia	Negative
2019	Tully[20]	USA	2007–2014	8.7[a]	325 (3.6)	8,792 (96.4)	NS	NS	All dementia	Positive
2019	Tae[66]	South Korea	2008–2015	4.1	12,712 (50.2)	12,620 (49.8)	71.2 ± 8.2	71.1 ± 7.8	All dementia	Positive
2019	Jayadevappa[16]	USA	1996–2003	8.3	59,480 (38.9)	93,238 (61.1)	75.2 ± 5.9	75.2 ± 6.4	All dementia	Positive
2020	Kang[67]	South Korea	2007–2013	5.2	30,953 (22.0)	109,742 (78.0)	67.9 ± 8.0	67.2 ± 8.5	All dementia	Positive
2020	Shim[18]	South Korea	2012–2016	4.0	3,201 (49.8)	3,228 (50.2)	72.8 ± 8.5	72.6 ± 7.3	All dementia	Negative

ADT, androgen deprivation therapy; NS, not specified; SD, standard deviation.
[a] Median value.

with ADT had only a minuscule (1%) risk of dementia (subdistribution HR, 1.01; 95% confidence interval, 1.01−1.02). Moreover, the risks of AD and dementia were not associated with the ADT duration under adjusted analysis.[15]

4.5. Possible reasons for the discrepancy and limitation of previous studies using large databases

Various reasons can be suggested for such conflicting results from the aforementioned studies using large databases examining the effect of ADT on cognitive function. First, these inconsistent results are likely due to the inherent limitations of the large database itself. The investigators of the different studies had inevitably selected subjects using different diagnostic codes as databases used in these studies were captured primarily to aid reimbursements or clinical usage rather than research, which therefore resulted in potentially biased, heterogeneous cohorts. Second, possibilities of unmeasured or unknown confounders exist (e.g., family history of dementia, smoking, alcohol, physical activity, and so on), which are usually not included in these studies using big data.[17] The reason for the discrepancy may not only just be because previous studies used different cohorts from one another but also because the results are derived from the analyses using different or omitted covariables as different results were reported by three studies from South Korea using cohorts based on the same database, NHIS. Two Korean studies reported a somewhat elevated risk of dementia or AD in LHRH agonist users compared with nonusers.[66,67] However, one demonstrated no relevant association.[18] Differences in covariables included in the adjustment exist in these studies; socioeconomic status, chronic obstructive pulmonary disease, and a few other medical histories were exclusively included in the latter study, demonstrating no elevated risk of dementia in patients undergoing ADT with LHRH agonists.[18] Third, the start of follow-up was different between patients with and without ADT in some studies.[14] The start of follow-up was the time of ADT initiation for patients with ADT, whereas it was the time of PCa diagnosis for those without ADT. This difference in the follow-up period may have introduced immortal time bias.[17,68] Patients without ADT may have a longer average follow-up period compared with those with ADT because some patients with ADT may have started treatment years after the diagnosis, which can inflate the ratio denominator, thereby overestimating HR.[17] Fourth, complexity of the cognitive function is another major obstacle to proceeding with accurate research. Without any external influences, cognitive function can be affected by differences in baseline interpersonal intelligence and neuropsychological tests.[69] Lastly, diversities of study design, methodologies, agent type, treatment duration, and follow-up duration can make it difficult to draw consistent conclusions on this issue.[70]

5. Conclusion

The progress in the treatment of PCa using LHRH agonists, which has been proven to improve survival outcomes, however, comes with the caveat that a larger population of older patients will face serious adverse effects of contemporary ADT such as cognitive dysfunction. Accordingly, it is likely that changes in androgen level somewhat have implications for cognitive function based on the previous work in animals and humans. However, present studies using common neuropsychological tests as well as retrospective, population-based studies based on diagnostic codes and textural analysis from large data sets showed conflicting results.

Simply concluding whether ADT causes cognitive dysfunction is difficult because of various complex factors that can affect patients' cognition. Moreover, the literature review, so far, and the conduct of

a large numbered, population-based research, enabled the speculation that the risk of cognitive dysfunction or dementia does not increase only by administering LHRH agonists for a few months. However, the cause and effects of association between ADT and cognitive dysfunction are still yet to be confirmed by repetitive, well-designed studies with properly adjusted covariables, a uniform assessment tool for cognitive function, and especially, long-term follow-up. Until then, physicians should be encouraged to discuss the possibility of cognitive decline—although not certain—with their patients before ADT, Also, once ADT is initiated, it is necessary to regularly assess patients' neurocognitive changes during follow-up and subsequent neuropsychiatrist referral with the emergence of cognitive dysfunction.

Conflicts of interest

Nothing to declare.

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