Review Article
Healthy aging and anti-aging treatments

pISSN: 2287-4208 / eISSN: 2287-4690
World J Mens Health 2022 Apr 40(2): 243-256
https://doi.org/10.5534/wjmh.210175

The World Journal of MEN's HEALTH

Impact of Testosterone on Alzheimer's Disease

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Alzheimer's disease (AD) is a neurodegenerative disease responsible for almost half of all dementia cases in the world and progressively increasing. The etiopathology includes heritability, genetic factors, aging, nutrition, but sex hormones play a relevant role. Animal models demonstrated that testosterone (T) exerted a neuroprotective effect reducing the production of amyloid-beta (Aβ), improving synaptic signaling, and counteracting neuronal death. This study aims to evaluate the impact of T deprivation and T administration in humans on the onset of dementia and AD. A search was conducted on MEDLINE and Scopus for the "androgen deprivation therapy" and "testosterone therapy" with "dementia" and "Alzheimer's." Studies lasting twenty years with low risk of bias, randomized clinical trial, and case-controlled studies were considered. Twelve articles on the effect of androgen deprivation therapy (ADT) and AD and seventeen on T therapy and AD were retrieved. Men with prostate cancer under ADT showed a higher incidence of dementia and AD. The effect of T administration in hypogonadal men with AD and cognitive impairment has evidenced some positive results. The majority of studies showed the T administration improved memory and cognition in AD while others did not find any benefit. Although some biases in the studies are evident, T therapy for AD patients may represent an essential clinical therapy to reduce dementia incidence and AD progression. However, more specific case-controlled trials on the effect of androgens therapy in men and women to reducing the onset of AD are necessary.

Keywords: Alzheimer disease; Amyloid beta-peptides; Dementia; Estradiol; Neuroprotection; Testosterone

INTRODUCTION

Alzheimer's disease (AD) is a devastating neurodegenerative disease responsible for almost half of dementia cases [1] and progressively increasing with upper of 50 million people affected. Etiopathology of AD is multifactorial, including genetic factors and heritability, nutritional disorders, mitochondrial dysfunction, oxidative stress, and aging [2]. AD is characterized by an abnormal Aβ deposition in neuron and extracellular plaque formation responsible for the pathologic events, causing neuronal degeneration [3] and synapsis dysfunction [4]. Aβ deposition and the regulation of amyloid-beta (Aβ) protein precursor is regulated mostly by testosterone (T) pathways and are described in another review [5].

Sex hormones play a relevant role in developing AD, as evidenced by the greater incidence in women than men [6]. In cellular [7] and animal models of AD [8,9], it was demonstrated that T level was closely associated with the neuronal efficiency and reduced the Aβ deposition in the brain. By activating AR signaling pathway, T stimulates the microglia phagocytosis, removing the Aβ deposition and inhibiting the inflammatory re-

Received: Aug 31, 2021 **Revised:** Sep 16, 2021 **Accepted:** Sep 23, 2021 **Published online** Jan 2, 2022
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sponse [10]. In the rat model of AD, it was shown that T prevented cognitive decline scavenging free radicals, thereby enhancing synaptic plasticity [9,11], and regulates neuronal bioenergetic increasing mitochondrial function [12], increasing antioxidant activity preventing neurodegenerative disorders. Furthermore, T reduces insulin-resistance in obesity, improving cognitive function [13]. Furthermore, T prevented vascular and neuronal aging by increasing eNOS activity and stimulating SIRT1 expression [14]. The behavioral performance and learning was associated with an increased SYN expression levels [15]. Dihydrotestosterone (DHT) appeared to be more effective treatment to reduce the onset of dementia [16].

In men, low serum T levels have been implicated in the pathogenesis of AD [17]. In contrast, a higher serum level of free T in both sexes seems to be protective against AD incidence and development [18]. Lee et al [18], in older subjects, evaluated by B-positron and magnetic resonance imaging, and found that a high free T level in females and males was correlated with lower cerebral Aβ deposition and lower cognitive impairment, while free estradiol was not related to Aβ or neurodegeneration in both sexes. This study evidenced that T is active in the early stage of the pathological accumulation of Aβ. Other studies showed that men's low T serum levels were associated with an increased Aβ deposition, causing AD development [18,19] and synaptic dysfunction with a consequent cognitive decline [4]. Considering the high impact of T on maintaining brain health, this study aims to evaluate the effect of androgens deprivation and treatment on the evolution of AD.

EFFECT OF TESTOSTERONE ON ALZHEIMER'S DISEASE

The wide distribution of androgen receptors (ARs) in the brain suggests that androgen may exert a relevant role in neuronal function. AR is mainly expressed in the hypothalamus and amygdala, areas deputies to learning and memory, in the telencephalon, amygdala, and spinal cord [20]. The neurotrophic effect of T consists of activating AR and preventing Aβ deposition on neurons directly and by the action of its metabolite 17β-estradiol [21]. T improves energy metabolism and reduces oxidative stress in neurons [22] and down-regulates the beta-secretase (BACE1) enzyme activity, enzyme that reduces the Aβ deposition, suggesting that endogenous T, independently from estrogen, may protect against AD in males [23]. The effect of T on cellular bioenergetics is more efficient than other sex hormones, such as progesterone and estrogens [24]. The action of T on neurons is complex and regulated by its direct action associated with the effects of the various metabolites originated by T molecule. T and its related neurosteroids (structurally diverse neurosteroids such as progesterone, estradiol, estrone, T, 3alpha-androstanediol [3α-Diol], DHEA, and allopregnanolone) are involved in the regulation of neuron activity [25].

T can be aromatized in 17β-estradiol, in DHT after the 5α-reductase effect, and androstenedione after the partial reduction by 3α-HSOR converted to 3α-Diol, which has estrogenic effect, which activates the GABA receptors. 17β-estradiol activates estrogen receptors (ERs), potentiating some effects of T. Metabolites of T, such as DHT and Androstenediol show interesting differences in their relative biologic effects in the activation of the AR.

However, T has a direct neuroprotective effect, independently by its conversion into estradiol [23], potentiating the anti-Aβ effect and reducing the neuronal death of 80% to 90% [26]. The metabolite 3α-Diol is of relevant interest because it is potent GABA(A) receptor-modulating neurosteroids with anticonvulsant properties, and 3α-diol production, but not T, restores cognitive and affective performance [27]. Androstenediol is active on GABA and N-methyl-d-aspartate (NMDA) receptors responsible for memory, learning impairments, and psychosis. Notably, the 5α-androstane, 3β,17β-diol (3β-Diol) activate ER and not AR. The NMDA receptor RNA is also influenced by the GH and insulin-like growth factor-1 (IGF-1) levels that increase the expression and are more prominently affected by chronological age than by the sex hormones (Fig. 1) [28].

T influences cognition, enhancing synaptic plasticity [11], increasing the number of intact cells and the dendritic spine density in the hippocampal region [8]. Castration reduced the hippocampal dendritic spine density, which is restored by androgen administration. In the presence of low serum T levels, many biochemical and metabolic functions in the brain are compromised (Fig. 1).

A meta-analysis showed that low plasma T level was significantly associated with increased risk of AD, and it should be considered a risk factor in worsening cog-

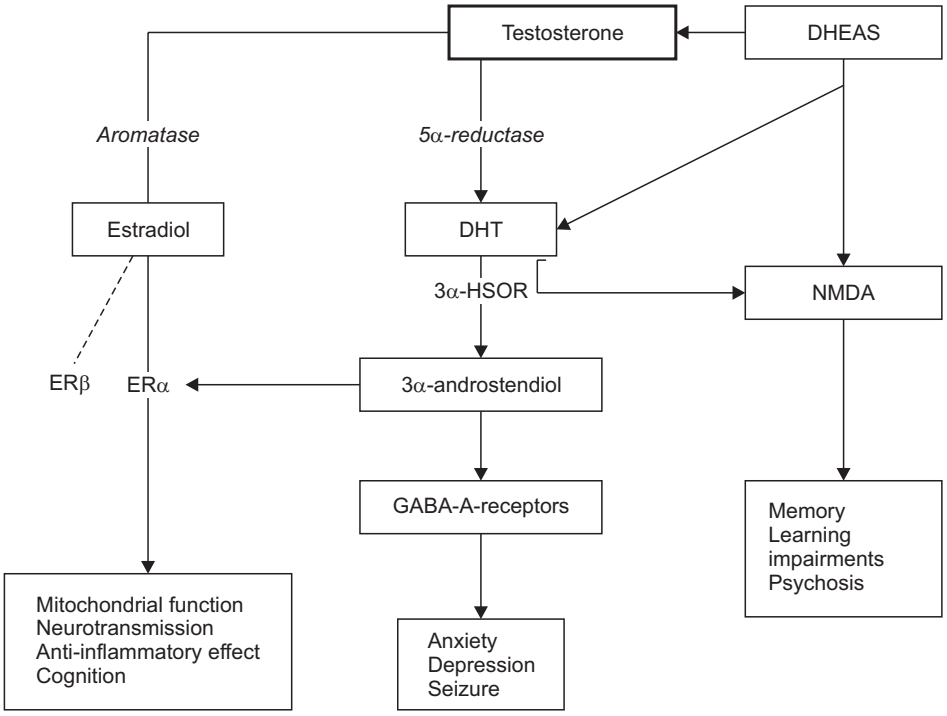

Fig. 1. Testosterone, the effect of α-reductase, is reduced to DHT, the strongest non-aromatizable androgen. DHT is then in Androstenediol from which metabolites 3α- and 3β-diol have a weak effect on AR while are more active on Erα and Erβ. 3α-diol activates GABA-receptors which regulate anxiety, depression and seizure. Testosterone is also aromatized in 17β-estradiol which, activating Erα and β, stimulates mitochondrial function, neurotransmission, and anti-inflammatory effect with consequent improved cognition. DHT and DHEAS activate the NMDA receptors which regulate memory, learning impairment, and psychosis. DHT: dihydrotestosterone, NMDA: N-methyl-d-aspartate, AR: androgen receptor.

nitive function in elderly men [17].

THE ROLE OF ESTRADIOL

The mouse model demonstrated that estradiol exerted an essential role in regulating endogenous neurogenesis, synaptic plasticity, and cognitive function in the early stage of AD [29] and protected the young APP/PS1 mice from cognitive decline [30]. In women, estrogens exert a protective role against neurodegeneration, and with the onset of menopause, the drop-in plasma level is considered a determinant factor in AD development. In menopausal women, plasma serum androgens and SHBG decline progressively with advancing age [31,32]. Consequently, estradiol derives primarily from the aromatization of T in extra-gonadal tissue and is regulated by the aromatase expression in the tissues [33]. The medium plasma level of androgens in women significantly decreases with advancing age. The plasma level of total and free T in the range of age 65 to 74 compared to the range of 18 to 24 years varies from 1.8 to 0.66 nmoL/L, and 23.61 to 10.81 pmoL/L respectively. DHEAS and Androstenedione also decreases of one-third [31].

However, whether estrogens administration in menopausal women to prevent AD was effective remains questionable. Although some observational studies found a reduced incidence of AD and dementia between women taking estrogen therapy [34-36], others did not find any positive effect [37,38]. A recent study on a large population of 84,739 postmenopausal women showed that the systematic administration of estrogens was associated with an overall increased incidence of AD [39]. Although possibly beneficial if taken during a critical window near menopause, estrogens therapy (especially opposed compounds) initiated in later life may be associated with increased risk in A.D. Placebo-controlled trials reported an increased risk of the incidence of dementia in women who received a conjugated equine estrogen independently from the association of medroxyprogesterone acetate [40]. Tolppanen et al [41] did not find any differences in systemic estrogen use among Finnish women with AD than those without AD. The relation of AD risk to timing and type of hormone replacement deserves further study [42].

The higher incidence of AD in women is related not only to estrogen activity but also to the plasma level of androgens and this may explain why women are at increased risk of cognitive decline and AD compared with men.

Estrogens exert a different, when not opposite, effect on the brain in males and females [43]. The estrogen action is not related only to the plasma levels but also to those synthesized in non-reproductive tis-

sues, particularly in the brain, and has cell-specific estrogen synthesis and ER signaling [44]. Tibolone, a synthetic hormone with estrogenic, androgenic, and progestogenic activity, showed a neuroprotective effect [45]. Although few studies on the impact of tibolone on Central Nervous System, it improved memory and learning [46-48]. These studies suggest that the association of T with estrogen can probably be relevant in the treatment of AD, considering that T can be aromatized at the cellular level. Furthermore, the neuroprotective actions induced by estrogens are interlinked with the IGF-1 signaling pathway [49] that should be considered in the evolution of AD. In conclusion, the effects of 17β-estradiol on the brain *per se* is complex because is not only evaluable by its serum level, but the formation at cellular level seems more effective, and they would be evaluated concerning the plasma level of androgens and IGF-1.

METHODS

The search was conducted, finding out on MEDLINE and Scopus from the year 2000 until now, clinical studies with the following keywords: "androgen deprivation therapy" with "Alzheimer's disease," and "dementia" and "Alzheimer's disease" and "testosterone therapy" with AD.

RESULTS

For androgen deprivation therapy (ADT) and dementia, twenty articles (Table 1) and seventeen for T therapy and AD (Table 2) were retrieved. Inclusion criteria were absence of history of cancer before the diagnosis of prostate cancer or those who received both orchiectomy and GnRH agonist.

ANDROGEN DEPRIVATION THERAPY AND DEMENTIA

Twenty studies conducted on large cohorts of patients have investigated the effect of ADT on the risk of developing AD or dementia have been selected [50-69]. The studies are summarized in Table 1. The majority (13 studies) found a significant association between ADT with cognitive function and dementia [50-54,56,57,60,63,64,66,68,69], while others did not [55,58-62,65,67]. The type of therapy plays a despaired effect on AD [51]. Longitudinal studies evidenced that in men with prostate cancer (PC) treated with antiandrogen therapy, the plasma T level decreased while the Aβ level increased [19,70]. Systematic reviews demonstrated that men with PC under ADT have a higher risk of cognitive impairment and dementia [71] and worsening depression [72] confirmed by a recent meta-analysis [73].

The controversial results that emerged from the studies show the complexity of the investigation on ADT's effect on brain efficiency and dementia. Baik et al [60] investigated a population of 1,238,879 patients, of which 35% underwent either chemical or surgical ADT in a follow-up of an average of 5.5 years, and they did not find any correlation between ADT with AD. However, the study lacked of essential information; there was no account for the use of antiandrogens, family history of AD, smoking habits, and PC staging information and biomarkers. Notably, the routine therapy used by the patients was not taken into account. Furthermore, a specific test to evaluate cognitive state was not performed. Chung et al [67] demonstrated in a large population that ADT was not correlated with increased incidence of AD or Parkinson's disease. However, data were retrieved from an extensive insurance database (5,340 subjects) and patients were tracked for 5 years and received the diagnosis from their index database. No specific information about the patients was given, familiarity, correction for confounding factors such as body weight, diabetes. We individually tracked each patient (n=5,340) for a 5-year period (from the years 2001 to 2013) to discriminate those who subsequently received a diagnosis of AD, starting from their index date.

These data suggest the complexity of drawing significant conclusions from a large population study. The study of Nead et al [73] conducted on a population of 16,888 individuals with PC supported a statistically significant association between ADT use and AD and with the duration of ADT. The methodology of the study was accurate. Men who received chemotherapy were excluded because chemotherapy was associated with cognitive dysfunction and an expected high correlation between receipt of chemotherapy and ADT use. Patients with a history of dementia were considered, and only those who started the follow-up after initiation of ADT were included. The selection of the patient's group of investigation is essential to reduce to risk of bias. Large cohorts of patients suffering from

Table 1. Effect of ADT on cognitive impairment and AD development

Study	Patients	Age (y)[a]	Study	Observational time	Clinical outcomes
Hong et al, 2020 [50]	24,464 men with PC	ADT 74.1 Non-ADT 71.0	Cohort study	4.98 years	ADT was significant associated with overall risk of cognitive decline.
Huang et al, 2020 [51]	23,651 men with PC	73	Cohort study	-	ADT was associated with an increased risk of dementia or AD. GnRH agonist and orchiectomy had no significant difference compared with patients who did not receive ADT.
Jayadevappa et al, 2019 [52]	154,089 men with PC	76	Retrospective studies	8.3 years	ADT exposure was associated with subsequent diagnosis of AD or dementia.
Krasnova et al, 2020 [53]	100,414 men with PC	73	Observational	6 months	ADT was associated with a higher risk of all-cause dementia, AD.
Jarzemski et al, 2019 [54]	100 PC prostatectomy	50–77	Observational	-	Complex therapies induced a significantly worse result of deferred memory and psychological burden.
Robinson et al, 2019 [55]	25,967 men with PC, 121,018 controls	76.5	Population-based cohort study	4 years	No increased risk of Alzheimer's dementia for men on ADT.
Tae et al, 2019 [56]	35,401 National Insurance Service	70	Follow-up	7 years	ADT correlated with an increased risk of cognitive dysfunction.
Nguyen et al, 2018 [57]	201,797 men with PC (94,528 patients received ADT)	66	Follow-up	19 years	ADT was associated with higher risks of bone fractures, diabetes, dementia, CHD.
Marzouk et al, 2018 [58]	81 PC	69	Cohort studies	1 year	ADT was not associated with self-reported cognitive function decline in non-metastatic PC.
Deka et al, 2018 [59]	45,218	Not reported	Observational cohort study	6.8 years	No statistically significant increase in the risk of any dementia or AD.
Baik et al, 2017 [60]	109,815 men with PC	67	Survival analysis	-	Risks of AD and dementia were not associated with the duration of ADT.
Alibhai et al, 2017 [61]	77 PC with ADT 82 PC without ADT 82 controls	68.9	Case-control studies	3 years	ADT was not associated with cognitive decline.
Kao et al, 2017 [62]	755 PC	74.2	Follow-up	5 years	No difference in the incidence of dementia in patients who receive ADT.
Gunlusoy et al, 2017 [63]	78 metastatic PC 78 controls	67.1 68.6	Prospective studies	1 year	ADT affects cognitive functions such as language ability, short-term memory capacity, mental flexibility.
Nead et al, 2017 [64]	9,455 men with PC	69.9	Observational cohort study	3.4 years	ADT was associated with an increased risk of dementia.
Khosrow-Khavar et al, 2017 [65]	30,903 men with PC	70.7	Follow up	4.3 years	ADT was not associated with an increased risk of dementia.
Wu et al, 2016 [66]	19 ADT 20 controls	67.5 70.0	Retrospective studies	-	ADT patients are more vulnerable to experiencing specific cognitive and neurobehavioral symptoms.
Chung et al, 2016 [67]	1,335 PC 4,005 controls	72.2	Retrospective studies	5 years	ADT in PC was not associated with a higher risk of Alzheimer's and Parkinson's disease.
Nead et al, 2016 [68]	16,888 men with PC	70.0	Retrospective studies	2.7 years	ADT increased the risk of AD in a general population cohort.
Gonzalez et al, 2015 [69]	58 ADT 84 no ADT 88 controls	67.3 67.7 69.1	Comparative study	5 years	ADT demonstrate impaired cognitive performance within 6 and 12 months.

ADT: androgen deprivation therapy, AD: Alzheimer's disease, PC: prostate cancer, CHD: coronary heart disease.
[a]Values are presented as mean only.

Table 2. Effect of testosterone therapy on AD and cognitive impairment

Study	Patients	Age (y)[a]	Study	Therapy	Duration	Outcomes
Resnick et al, 2017 [77]	788 men, impaired sexual function	65	RCT	T gel with a dose to maintain the physiological plasma level	4 years	No association with improved memory or other cognitive functions.
Wahjoepramono et al, 2016 [78]	44 men	≥50	RCT	T gel 50 mg	24 weeks and 4 weeks washout	Significant improvement in general cognitive functioning.
Huang et al, 2016 [79]	308 men with low T	60	RCT multicenter study	T gel 7.5 g of 1%	36 months	T administration did not improve cognitive function.
Asih et al, 2015 [80]	44, older men	61±7.7	RCT	Transdermal T (50 mg/d)	24 weeks	Significant increases in plasma androgens levels. No changes in plasma amyloid-beta. Dementia is not investigated.
Cherrier et al, 2015 [81]	351 men community 37 with MCI and low T	70.5±8.2	RCT	T gel (50 to 100 mg/d)	3 months	Modest improvement in verbal memory and depression symptoms.
Borst et al, 2014 [82]	60 hypogonadal men	70.8	RCT	T-enanthate (125 mg/wk)	12 months	Small improvements in depressive symptoms and visuospatial cognition.
Young et al, 2010 [83]	26 young 62 older	25–35 60–80	RCT	GnRH agonist, T-gel 75 and 100 mg	6 weeks	Free T positively correlated to spatial cognition while estradiol negatively correlated with working memory.
Emmelot-Vonk et al, 2008 [84]	237 healthy men with a low T level	60–80	RCT	T undecenoate 80 mg	6 months	Cognitive function and bone mineral density did not change.
Vaughan et al, 2007 [85]	65 healthy men		RCT	200 mg of T every 2 weeks with 5 mg of finasteride daily (T+F), or placebo	36 months	No clinically significant effect on tests of cognitive function.
Maki et al, 2007 [86]	15 normal men	66–87	RCT	T enanthate (200 mg i.m. every other week)	3 months	Decreased verbal memory and altered relative activity in medial temporal and prefrontal regions.
Cherrier et al, 2007 [87]	57 eugonadal men	67±11	RCT	T enanthate i.m. 50, 100, or 300 mg/wk	6 weeks	No significant changes in memory.
Lu et al, 2006 [88]	16 men with mild AD		RCT	T gel (75 mg)	24 weeks	T replacement therapy improved the quality of life in AD patients. T had minimal effects on cognition.
Haren et al, 2005 [89]	76 healthy men	60	RCT	T undecanoate 80 mg twice daily	12 months	Not affect scores on visuospatial tests or mood and quality of life scales.
Kenny et al, 2004 [90]	11 men with cognitive decline	80±5	RCT	200 mg every 3 weeks	12 weeks	No significant changes in behavior, function, depression, or cognitive performance.
Tan et al, 2003 [91]	36 men with AD 10 hypogonadal		RCT	Intramuscular T 200 mg every 2 weeks	12 months	ADAScog, MMSE, and CDT improved significantly in treated patients.
O'Connor et al, 2001 [92]	30 healthy eugonadal men and 7 hypogonadal men		RCT	200 mg of T enanthate i.m. weekly	8 weeks	Increased T has a differential effect on cognitive function, inhibiting spatial abilities while improving verbal fluency.
Cherrier et al, 2001 [93]	25 healthy men		RCT	T enanthate 100 mg weekly	6 weeks	Short-term T administration enhances cognitive function.

AD: Alzheimer's disease, RCT: randomized controlled trial, T: testosterone, MCI: mild cognitive impairment, GnRH: gonadotropin-releasing hormone, ADAScog: Alzheimer's Disease Assessment Scale Cognitive Subscale, MMSE: Mini-Mental Status Examination, CDT: clock drawing test.
[a]Values are presented as mean only or mean±standard deviation.

PC analyzed heterogeneous populations, including patients with different cancer progression stages, and palliative treatment can include various confounder factors, like pain, chemotherapy, and psychosocial and emotional stress. Memory declines under emotional conditions, such as depression and anxiety, and chronic psychosocial stress [74] that can trigger AD [75].

Furthermore, tests to investigate mental disorders were not regularly applied with the same methodology. Finally, yet significantly, nutritional needs and hormones such as estradiol and IGF-1, which are generally not considered in the studies, influence significantly the memory decline. Different modality of treatment is associated with a high risk of bias in the research and false results. No significant cognitive decline changes were found in men with PC who received ADT treatment by radiotherapy [59].

ADT consists of different methodologies, including bilateral orchiectomy or drug treatment using gonadotropin-releasing hormone (GnRH) agonists, antiandrogens, or combination therapy [50]. The various forms of ADT have a different effect on the hypothalamic-pituitary-gonadal axis than can affect dementia development.

Kao et al [62] in the Chinese population find no correlation between ADT and incidence of dementia, particularly ADT with GnRH agonists and without GnRH agonists. This may contribute to the variability of the effects in studies evaluating dementia. Hong et al [50] found that the cognitive decline was higher in patients receiving antiandrogens therapy than those who underwent combined androgen blockade, bilateral orchiectomy, GnRH agonist, and non-ADT treatment. In men, the androgen blocked therapy due to PC, a significant rise in the plasma levels of Aβ, and increased depression and anxiety scores were found [19].

Factors affecting cognitive decline that interact with ADT are not only physiologic but also include mood and fatigue, particularly in patients who face a high risk of death from disease, and neurocognitive decline is reasonable [76]. The cognitive decline in the elderly is a tricky clinical aspect to evaluate, and many emotional and psychological factors can be conditioning. Particularly in the studies conducted on a large population, the risk of bias should be considered. Cognitive symptoms detected with the neurophysiological test can be easily confused with psychological symptoms [66].

EFFECT OF TESTOSTERONE THERAPY ON COGNITION IN PATIENTS WITH ALZHEIMER'S DISEASE

The effect of T administration to improve cognition and reduce the progression of AD have been investigated in seventeen studies selected (Table 2) [77-93]. Some studies showed positive effects of T therapy on certain cognitive domains in normal and hypogonadal older men [78,81-83,88,91-93], while others had no conclusive results [77,79,84,85,87,90.].

Most studies that did not improve cognition and memory were conducted on a relatively healthy population (60–65 y) with sexual impairment, but not cognitive impairment. T administration was transdermal gel varying from 90 days until 4 years. Resnick et al [77], on a large population of 788 men, 65 years old, with sexual impairment, did not find any effect of T therapy on memory and cognitive function. Treatment consisted of T gel for 90 days to restore the physiological plasma T levels. Huang et al [79] T gel treatment in men 60 years old with low plasma T level and did not improve memory. Asih et al [80] found similar results in 61-year-old men with transdermal T administration. Emmelot-Vonk et al [84] investigated healthy men per 6 and 36 weeks administrating 80 mg of T undecenoate orally did not evidence any cognitive improvement. Cherrier et al [81] evaluated a small group of hypogonadal men with mild cognitive impairment, found only a modest improvement in verbal memory.

T therapy includes a wide range of doses varying from transdermal (gel 7.5 g of 1%), oral (80 mg/day), and intramuscular (200 mg/weekly), and this contributes to substantially different clinical outcomes.

Maki et al [86] found that T enanthate (200 mg i.m. every other week in ordinary men decreased verbal memory. However, the number of patients was very restricted; only 15 subjects and the study has some risk of bias. Various systematic reviews showed that low plasma T level may be associted with a reduced cognitive ability and T therapy exerted positive effects on cognitive function in normal and hypogonadal elderly men [94-96].

Verdile et al [97], in 427 men with cognitive impairment, found that LH and plasma free T inversely correlated with plasma Aβ level and brain amyloid deposition through the highly imaging, biomarkers and

lifestyle study. The histopathology analysis of postmortem brain tissue in postmenopausal women showed no changes in androgen and estrogen levels. In contrast, women with AD androgen and estrogen levels were low, indifferently from the age of patients. In the male brain, aging was correlated with low androgen and estrogen levels. In those with advanced AD and brain dysfunction, the brain T levels, but not estrogen, were significantly reduced [98]. Noteworthy, in patients with memory loss, the Aβ level was correlated with total and free T levels [99]. The problem of a standardized approach to assessment is determinant.

DISCUSSION

Although animal models have demonstrated the effect of T in the reduction of βA deposition and the development of AD in the brain, in human subjects remains not homogeneous.

Majority of studies showed that ADT in patients with PC compromises cognition and increases the risk of PD. Not all ADT treatments have the same effect. Chemotherapy and androgen depressant drugs had the most deleterious effects, while LHRH inhibitors seem less involved in the cognition worsening process. Urologists when starting the therapy program should consider this clinical aspect.

Many clinical evidences showed that subjects with a low androgens level are at higher risk of cognitive decline [100], memory loss, attention deficit, and motor function in multiple sclerosis [100-102] and AD [88]. A progressive reduction of serum level of LH and T in the early preclinical stage may be considered prognostic of AD risk [97]. The prevalence of studies clearly showed that physiological plasma T levels are necessary to maintain brain function, and reduced plasma T levels predispose to dementia and AD, remarkably free T level, may predispose to cognitive decline and increased risk of AD [103]. These neurologic dysfunctions were observed before the diagnosis [104]. The most significant cohort studies found that ADT in men with PC were correlated with a higher incidence of AD [50-53,57]. ADT should be specified in which methodology it was done: antiandrogens, chemotherapy, GnRH, because each treatment exerts a different clinical effect. It can be assumed that androgens play a protective role in maintaining neuron integrity and functional integrity. T's neuroprotective effect is expressed at cellular lev by increasing mitochondrial efficiency, improving the cellular bioenergetics more efficiently than other sex hormones, such as progesterone and estrogens [24]. The expression of AR, ERα, and aromatase is markedly reduced in hypogonadal men and men with type 2 diabetes, concerning eugonadal, but T replacement can reverse these deficits [105], contributing to significantly reduced cellular responses to sex hormones. The aromatase reduced activity is a critical factor for the 17β-estradiol production at cellular level.

However, the effects of the T administration in patients with AD evidenced controversial results. With the discrepancy in the hazard ratio, a better understanding of the methodological differences among studies should be uniformed. One of the most critical aspects in the methodology is represented by the dose of administration of T and adherence to therapy. The adherence to therapy is essential to maintain a regular plasma level of hormone. However, only 38.7% of the patient using T therapy met the criteria and the discontinuation time differed significantly among formulations that was longest among recipients of oral [106] and topical treatment [107]. T gel that can provide a low serum level and then be ineffective because a dose-dependent improvement on memory has been demonstrated [108]. T injections may be more efficacious than topical administration, as reported by Skinner et al [109]. Long-term follow-up, especially in men with mild cognitive impairment, may only be achievable with long-acting preparations (injections of T undecanoate or T pellet implants) administered by the investigator or treating physician.

Furthermore, the plasma level of free T and 17β-estradiol is necessary to evaluate the effect of the therapy. After T administration, it is essential to determine its metabolites because they help maintain neuronal efficiency, such as 17β-estradiol, DHT. Although patients receive the same T treatment, they may have a different clinical effect due to T's different absorption and metabolism (Fig. 1).

Secondly, T administration's effects have been evaluated in healthy men, hypogonadal men, and only a few studies assessed AD patients' impact [88,110]. Both found an improvement in clinical outcomes.

A recent review evidenced that T administration positively affected some cognitive domains in normal and hypogonadal older adults [94], and the clinical effect was small [111].

Another critical aspect of these studies examines the relationship between global cognition evaluation with the Mini-Mental State Examination (MMSE) and T levels. Although the test is widely used, the determinations are not sensitive to slight/subtle changes in cognition, particularly in healthy subjects and community-dwelling people [112]. Furthermore, only high levels of free T were associated with global cognition evaluated by MMSE, and a non-linear relationship between MMSE score and total T level was observed. Another critical aspect is depression, which is a clinical condition detrimental to the hippocampus and may alter a mental test.

Of relevance, T level regulates AR and ER expression in the tissues, and aromatase activity is significantly reduced in men with low T levels [105].

Besides T, other androgens can be used as neuroregeneration therapy in men and women, such as synthetic androgens (oxandrolone, stanozolol, nandrolone, *etc.*) and the selective androgen receptors modulators (SARM), which have a relevant neuroprotective effect in AD [113] and this potential therapeutic applications are still being explored.

However, T treatment may need to be long-term and require monitorization to maintain T serum level at physiological levels and its metabolites. It is possible that a combination of T therapy together with a healthy lifestyle approach, including improved diet and exercise, may significantly reduce AD risk [114].

Essential confounding factors, generally not considered, are nutrition, body composition [115], and physical exercise that may significantly reduce cognition decline in older adults with AD [116,117] and the disease progression [118].

Some studies' weak association between T and AD may reflect inverse etiological mechanisms, risk of bias, or insufficient or inappropriate control for potential confounding factors.

FUTURE PERSPECTIVE

Studies conducted on a large population, with a more specific approach to assessment adequately cognitive performance and cause-effect of T administration in AD, correcting for the confounding factors and including the evaluation of plasma levels of the total and free T, 17β-estradiol, and IGF-1 are required. Another relevant problem in medical research is related to the lacking of a dedicated population in clinical trials.

CONCLUSIONS

Although some clinical discrepancy exists between the studies, androgens significantly impact brain function and are beneficial in patients with AD. Low circulating androgen levels should be considered a substantial risk factor for AD development and memory loss. T administration in men with low plasma T levels enhances global cognitive performance, memory, and executive function and the treatment should be start at the early phase of the disease. In men and women with AD or mental impairment, androgens may improve the mental condition and reduce the progression of AD, exerting a protective effect.

Conflict of Interest

The authors have nothing to disclose.

Funding

None.

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