Review Article
Healthy aging and anti-aging treatments

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Testosterone Deficiency and Risk of Cognitive Disorders in Aging Males

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Cognitive impairment and dementia are predicted to undergo a dramatic increase in the following years with more than 131.5 million people being affected by 2030. Although vascular diseases play the most important role in the pathogenesis of memory impairment in aging men, some pre-clinical and clinical evidence has suggested a possible contribution of the age-dependent reduction of testosterone (T). In this paper we have summarized and discussed all the information derived from available animal and experimental studies. In addition, we meta-analyzed data rising from all randomized placebo controlled trials (RCTs) published so far. Only limited preclinical and clinical evidence can support a possible contribution of T in the pathogenesis of the age-dependent impairment of cognitive functions. In addition, our meta-analysis did not support the use of T replacement therapy for the improvement of several cognitive domains analyzed including attention/working memory, executive function, language, verbal memory, visual memory, visuomotor ability, and visuospatial ability. However, it is important to recognize that the vast majority of available RCTs included mixed populations of subjects with eugonadism and hypogonadism preventing any final conclusion being drawn on these issues.

Keywords: Aging; Cognitive impairment; Dementia; Hypogonadism; Testosterone

INTRODUCTION

Life expectancy has steadily increased over recent decades in all high-income countries. Data from members of the Organization for Economic Cooperation and Development, including a population of about one million people among all high-income countries worldwide, suggest that by 2030 life expectancy will increase with a probability of at least 65% for women and 85% for men [1]. In particular, projection data indicate that, for men, South Korea, Australia, and Switzerland will show the best results with a 95% probability that men's life expectancy at birth in these three countries will surpass 80 years in 2030, and 27% that it would surpass 85 years [1]. Gender differences are confirmed also by these data with women's life expectancy projections worldwide higher when compared to men [1].

Although global aging is the result of medical, social, and economic advances over disease, it also presents important challenges. In particular, aging people are

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characterized by chronic and progressive diseases requiring assistance during the activities of daily living. Accordingly, cognitive impairment and dementia prevalence are predicted to show a dramatic increase with a projection by 2050 of more than 131.5 million people being affected [2]. In line with these data, the economic burden of US$ 818 billion is expected to increase substantially over the next few decades [3]. In order to face this situation, the World Health Organization (WHO) in 2012 lunched a worldwide call among all the dementia stakeholders in order to finalize common solutions and plans to solve the problem [4]. This has eventually led to the organization of the first WHO Ministerial Conference on Global Action Against Dementia in March, 2015 [2]. Among the identified top ten research priorities, the most important were those related to prevention, identification, and reduction of dementia risk factors as well as those on delivery and quality of care for people with dementia and their caretakers [2].

It is quite clear that vascular diseases play an essential role in the majority of patients with dementia [5]. However, it is also important to recognize that dementia phenotype includes a wide spectrum of features with several underlying risk factors. The role of the endocrine system and, in particular, of sex steroids, is still conflicting. In men, an age-dependent reduction of testosterone (T) has been reported [6]. Late onset hypogonadism (LOH) is the most frequently used term to describe this phenomenon. A recent meta-analysis, including all available observation studies, has documented that reduced T is associated with an increased risk of cardiovascular (CV) morbidity and mortality [7]. Similarly, several data have documented a close relationship between age-dependent reduction of T levels and worse CV and metabolic profile [8-10]. In addition, both pre-clinical and clinical studies have also suggested a possible direct role of T in neuro-protective mechanisms [11,12].

The aim of the present study is to systematically summarize and discuss all the available evidence regarding the possible role of T in age-depended male cognition impairment and dementia. Both animal and experimental data as well as results derived from randomized placebo controlled trials (RCTs) will be considered. When possible a meta-analytic approach will be used.

METHODS

A comprehensive Medline, Embase, and Cochrane search was performed including the following words: ("testosterone" [MeSH Terms] OR "testosterone" [All Fields]) AND ("cognition" [MeSH Terms] OR "cognition" [All Fields]). Publications from January 1, 1969 up to December 31st, 2019 were included. When available, meta-analytic data were preferred. In addition, a new meta-analysis on the effect of T replacement therapy (TRT) on cognition parameters with only placebo RCTs was also performed.

PRE-CLINICAL EVIDENCE

Androgen receptors (AR) are widely expressed within the central nervous system. T, in its free form, is able to cross the blood barrier and to influence neuronal cells, acting through genomic and non-genomic pathways [11,12]. Data from animal *in vitro* and *in vivo* models have reported conflicting results regarding the possible role of androgens on neuroprotection. In fact both beneficial and deleterious effects have been reported [11,12].

1. *In vitro* studies

Data derived from primary neurons suggested that T can act in protecting or exacerbating experimental neuronal damage depending on the concentration [13-15]. In particular, supra-physiological concentrations (10 μM) can amplify glutamate-induced excitotoxic neuronal death, whereas protection has been observed at 10 nM [16]. Although indirect effects due to T aromatization to estradiol have been reported, some evidence has also documented a direct role of androgens thought AR [13-15]. Neurotophic effects of T have also been described [17,18]. Data obtained in cultures of human neuroblastoma cells showed that T was more effective in alleviating β-amyloid induced mitochondrial bioenergetic deficits, by regulating mitochondrial oxidative phosphorylation genes [19-21]. Finally, more recently, it has been reported that, under pathological conditions, astrocytes can mediate, at least partially, the neuroprotective effects of gonadal steroid hormones by reducing the release of pro-inflammatory molecules [11]. Given the side effects that sex steroids may have when administered systemically, a number of synthetic agonists of the receptors for gonadal steroid hormones in the nervous system have been developed, and may be considered for

clinical use after brain injury, as potential enhancers of the neuroprotective astrocytic functions [11].

2. *In vivo* studies

Similar to what has been observed *in vitro* studies, data obtained in aged rodents documented that, during stroke, maintaining T, or dihydrotestosterone, plasma levels within the low physiological range confers protection [22]. The latter effect was blunted by administration of the AR antagonist flutamide, suggesting AR-mediated mechanisms [22]. In other experimental animal models, T administration is associated with an increase in neuron somal size, neuritic growth, plasticity, and synaptogenesis in both motoneurones of the spinal nucleous of the bulbocavernous [23]. Finally, in male double-transgenic mice, the increase of T levels is associated with a correspondent decrease in β-secretase, an enzyme involved in the cleavage of the amyloid β protein precursor [24]. However, other authors reported that, in castrated male rats, high androgen levels exacerbate ischemic damage [25]. Similarly, a more recent study showed that chronic high-dose T administration impairs cognitive flexibility in a rat animal model [26].

Table 1. Comparisons of the available meta-analyses evaluating the relationship between androgen deprivation therapy and cognitive impairment

	McGinty et al (2014) [32]	Sun et al (2018) [33]
Inclusion criteria		
No. of trials included	14	6
No. of patients analyzed	414	
No. of controls analyzed	122	
Outcomes evaluated		
Visomotor domain	Yes	No
Attention/working memory	Yes	No
Executive function	Yes	No
Language	Yes	No
Verbal memory	Yes	No
Visual memory	Yes	No
Visuospatial ability	Yes	No
Any cognitive impairment retrospective studies[a]	No	Yes
Any cognitive impairment prospective studies[b]	No	Yes

[a]Scoring 1.5 or more standard deviations below published norms on 2 or more tests, or scoring 2.0 or more standard deviations below published norms on at least 1 test; [b]Defined using International Classification of Diseases-9 diagnostic or procedure codes or other system based identification scheme.

CLINICAL EVIDENCE

Aging is associated with an impairment of cognitive ability, including memory, attention, language and visuospatial ability [2-5]. Some authors have hypothesized that the age-related reduction in cognition and the T decline are temporally related, suggesting a possible role of low T in cognition impairment [27,28]. Accordingly, cognition impairment has been considered a possible component of LOH [10,28-31].

1. Chemical castration and cognition

Up to now, two systematic meta-analyses have evaluated the relationship between androgen deprivation therapy (ADT) and cognition (Table 1). The first study included 14 RCTs with only a limited number of subjects (n=417 patients and 122 controls) [32]. Total duration of ADT ranged from a mean of 23 to 31 months, whereas mean age of the ADT groups ranged from 63.2 to 71.0 years across study samples [32]. Overall, across studies, various neuropsychological tests were used, which are divided into seven cognitive domains (Table 2) [32]. The authors concluded that patients treated with ADT performed worse than controls or than their own baseline on visuomotor domain, with larger magnitude effect in studies with a shorter follow-up. No significant effect was observed on the other six cognitive domains, including attention/working memory, executive function, language, verbal memory, visual memory, and visuospatial ability [32].

A more recent meta-analysis included two prospective and four retrospective studies, accounting for 442 and 67,644 men, respectively. Men included in the prospective studies were younger (mean 67 to 69 years old) than those evaluated in the retrospective survey studies (70 to 75 years old) [33]. When only prospective studies were considered, no difference between case and controls was observed in the risk of developing cognitive impairment, according to the International Cognition and Cancer Task Force (scoring 1.5 or more standard deviations below published norms on two or more tests, or scoring 2.0 or more standard deviations below published norms on at least one test). Similarly no increased risk of cognitive impairment was observed as defined using International Classification of Diseases-9 diagnostic or procedure codes or on other system-based identification schemes (Table 2) [33].

2. Serum levels of testosterone and cognitive function in aging men

Different population-based studies have investigated a possible relationship between T levels and cognitive function in aging men (Table 3) [34-43]. The number of subjects included ranges from 310 to up to almost 6,000. Several studies have documented an association between androgen status and cognitive impairment. In particular, two studies showed that subjects with reduced total T levels have a cognitive impairment. In addition, two studies demonstrated an inverse correlation between calculated free T, and two with free T index (FTI), and impaired cognition. However, it is important to recognize that all the aforementioned studies used radioimmunoassays for T evaluation, which have demonstrated some problems of accuracy, especially in the presence of very low levels of T [44]. In addition, the use of FTI for the assessment of androgen status has been strongly criticized [45].

In apparent contrast with the aforementioned results, when mass-spectrometry was applied, the gold standard method for all steroid evaluation, no association between low T and cognitive problems was reported (Table 3).

Table 2. Effect size of several cognitive test and risk of cognitive impairment in men treated with androgen deprivation therapy or controls

Risk factor	McGinty et al (2014) [32][a]	Sun et al (2018) [33][b]
Attention/working memory	-0.07 (-0.67–0.53)	
Executive function	-0.06 (-0.80–0.67)	
Language	-0.19 (-0.82–0.43)	
Verbal memory	-0.05 (-0.47–0.37)	
Visual memory	0.22 (-0.19–0.63)	
Visuomotor ability	-0.67 (-1.17–-0.17)	
Visuospatial ability	0.06 (-0.55–0.56)	
Any cognitive impairment prospective studies[c]		1.57 (0.50–4.92)
Any cognitive impairment prospective studies[d]	NA	1.75 (0.49–6.25)
Any cognitive impairment retrospective studies[e]	NA	1.28 (0.93–1.76)

NA: not available.
[a]Effect size (95% confidence interval [CI]). [b]Odds ratio (95% CI). [c]Scoring 1.5 or more standard deviations below published norms on 2 or more tests; [d]Scoring 2.0 or more standard deviations below published norms on at least 1 test; [e]Defined using International Classification of Diseases-9 diagnostic or procedure codes or other system based identification scheme.

1) Interventional studies – testosterone trials

In 2003, the US National Institute on Aging funded a set of clinical trials in order to better clarify the benefit and possible risks of TRT in the aging male.

Table 3. Relationship between endogenous testosterone (T) levels and cognitive function in available population-based studies

Reference (year)	Study	Country	Population	Type of T assay used	Cognitive outcome
Barrett-Connor et al (1999) [34]	Rancho Bernardo	USA	547 men aged 59–89 years at baseline	Radioimmunoassay	↓ In men with reduced TT
Yaffe et al (2002) [35]	Study of osteoporotic risk in men	USA	310 men aged 50 years or older	Radioimmunoassay	↓ In men with reduced BT
Moffat et al (2004) [36]	Baltimore longitudinal study of aging	USA	1,148 men aged 32 to 87 years at baseline	Radioimmunoassay	↓ In men with reduced FTI
Fonda et al (2005) [37]	Massachusetts male aging study	USA	981 men aged 40–70 years at baseline	Radioimmunoassay	↔
Muller et al (2005) [38]		Netherlands	400 men aged 40–80 years at baseline	Radioimmunoassay	↓ In men with reduced TT
Geerlings et al (2006) [39]	Honolulu-Asia aging study	Honolulu-Asia	2,974 men aged 71 to 93 years at baseline	Radioimmunoassay	↔
Thilers et al (2006) [40]	Betula study	Sweden	1,107 men aged 35 to 90 years at baseline	Radioimmunoassay	↓ In men with reduced cFT
Yeap et al (2008) [41]	Health in men study	Australia	2,932 men aged 70 to 89 years at baseline	Radioimmunoassay	↓ In men with reduced cFT
LeBlanc et al (2010) [42]	Osteoporotic fractures in men study	USA	5,995 men aged 65 years or older at baseline	Mass spectometry in a random sample of 1,602 men	↔
Wu et al (2010) [43]	European male aging study	Europe	3,369 aged 40 to 79 years at baseline	Mass spectometry	↔

↓: impairment, TT: total T, BT: bioavailable T, FTI: free T index, ↔: no difference, cFT: calculated free T.

Table 4. Characteristics and outcomes of the randomized, controlled clinical studies included in the meta-analysis

Reference (year)	No. of patient	Trial duration (wk)	Age (y)	Type of population	T levels	Dose (daily)	Design	Randomization	Blinding	Drop-out	Intention to treat
Janowsky et al (1994) [52]	56	12	67.4	Aging men	Mixed	T patch 15 mg/die	Parallel	A	NA	NA	NR
Janowsky et al (2000) [53]	19	4	67.5	Aging men	Eugonadal	TE 150 mg/wk	Parallel	A	NA	NA	NR
Cherrier et al (2001) [54]	25	6	70.2	Aging men	Eugonadal	TE 100 mg/wk	Parallel	NA	NA	A	A
Kenny et al (2002) [55]	44	52	75.5	Aging men	Mixed	T patch 50 mg/d	Parallel	NA	NA	A	A
Kenny et al (2004) [56]	11	10	79.6	Mild to moderate CI	Mixed	TE 200 mg/3 wk	Parallel	NA	NA	A	A
Cherrier et al (2005) [57]	25	6	70.2	AD	Eugonadal	TE 100 mg/wk	Parallel	A	NA	A	A
Haren et al (2005) [58]	76	52	68.5	Aging men	Mixed	TU 160 mg/d	Parallel	A	A	A	A
Lu et al (2006) [59]	18	24	69.8	AD	Mixed	TG 75 mg/d	Parallel	A	NA	A	A
Maki et al (2007) [60]	15	36	73.9	Aging men	<8 nM	TE 200 mg/wk	Parallel	A	A	A	A
Vaughan et al (2007) [61]	47	156	70.8	Aging men	<12 nM	TE 200 mg/2 wk	Parallel	A	A	A	A
Emmelot-Vonk et al (2008) [62]	237	24	67.3	Aging men	Mixed	TU 160 mg/d	Parallel	A	A	A	A
Fukai et al (2010) [63]	24	24	81.0	Mild CI	Mixed	TU 160 mg/d	Parallel	A	NA	NA	NA
Borst et al (2014) [64]	30	52	70.5	Aging men	<10.4 nM	T patch 150 mg/d	Parallel	A	NA	NA	NA
Cherrier et al (2015) [65]	22	24	70.5	Mild CI	<10.4 nM	TG 50 to 100 mg/d	Parallel	A	A	A	A
Huang et al (2016) [66]	308	156	67.6	Aging men	Eugonadal	TG 75 mg/d	Parallel	A	A	A	A
Wahjoepramono et al (2016) [67]	44	52	61.1	Mild CI	<10.4 nM	TG 50 mg/d	Cross-over	A	A	A	A
Resnick et al (2017) [46]	493	52	72.5	Mild CI	<8 nM	TG 50 mg/d	Parallel	A	A	A	A

T: testosterone, CI: cognitive impairment, AD: Alzheimer's disease, TE: testosterone enanthate, TU: testosterone undecanoate, TG: testosterone gel, A: adequate, NA: not adequate, NR: not reported.

Hence, a set of seven, 52-week, randomized, placebo-controlled, double-blind trials, including overall 788 hypogonadal (total testosterone [TT]<9.4 nM) men older than 65 years were designed and planned. All men included in the active arm were treated with T 1% gel. One specific RCT, the Cognitive Function Trial, specifically investigated the efficacy of TRT on cognitive outcomes among 493 men with age-associated memory impairment [46]. The primary designated outcome of the study was verbal memory, as assessed by delayed paragraph recall performance. The latter test was selected based on prior findings in small RCTs and on its clinical importance. In fact, epidemiological data indicate that, in the years preceding clinical dementia, verbal memory impairment is accelerated [47,48]. In addition, it is important to recognize that delayed paragraph recall performance involves neurological areas of the hippocampus, which contains both androgen and estrogen receptors, supporting a physiological role of sex steroids [49,50]. However, despite this evidence, TRT for one year, as compared with placebo, was not associated with improved memory, as well as with the other cognitive functions evaluated, including visual memory, spatial ability, and executive function [46]. In the T trials the cognitive function test was also used in subjects without memory problems. When the analysis was extended to the whole population, T-treated men showed a small, but statistically significant, increase in executive function. However, the same authors recognized that treatment effect was small and the observed result does not justify the use of TRT in older men to improve cognition [51].

2) Interventional studies – meta-analysis of available randomized placebo controlled trials

Besides the T trials, several other RCTs have evaluated the effect of TRT on cognitive function in aging men. In particular, 17 studies are available overall [46,52-67]. These trials enrolled 1,438 patients with a mean age of 70.4 years and a mean follow-up of 45.6

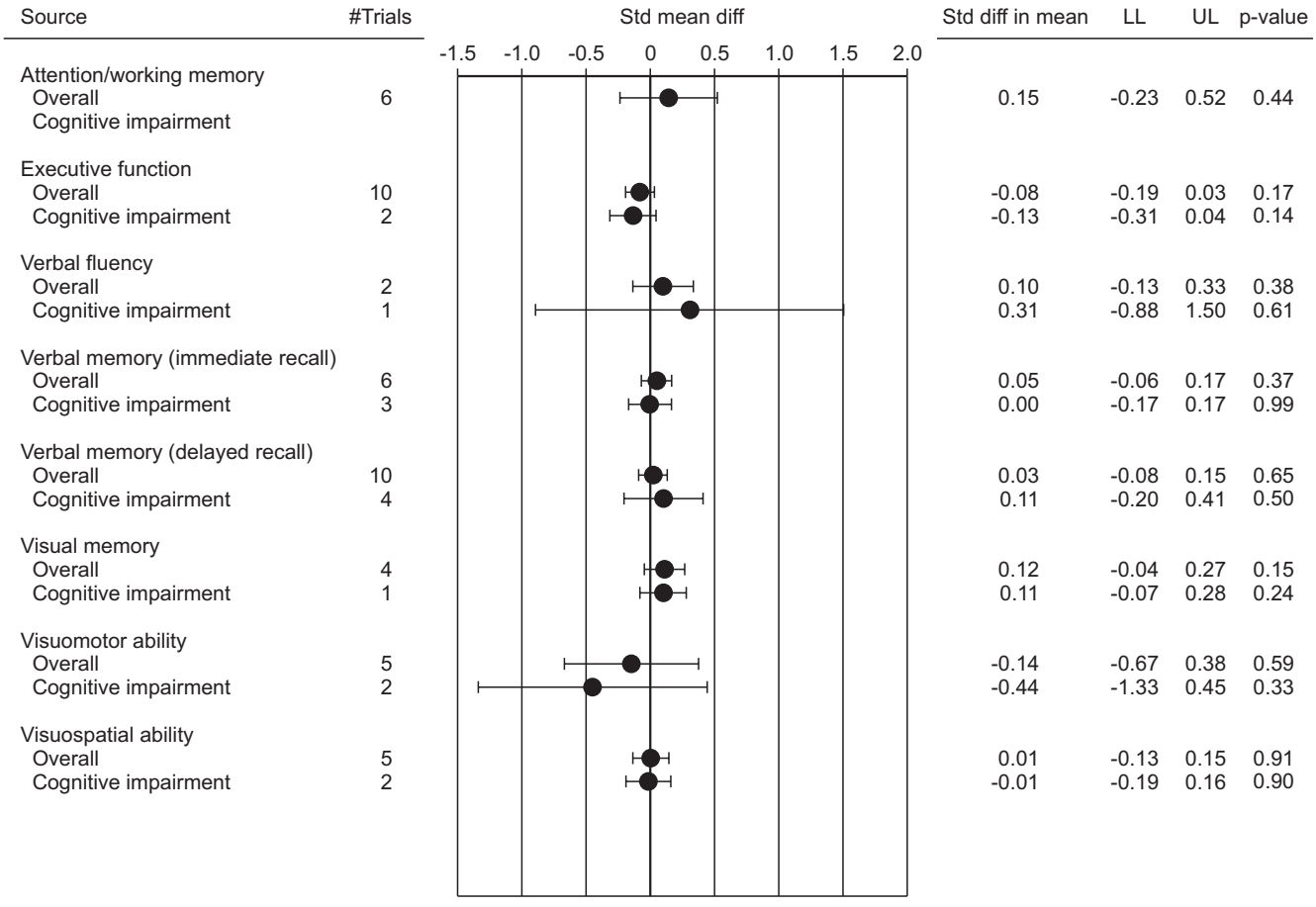

Fig. 1. Weighted standardized mean diff (with 95% confidence interval) of several cognitive domains at end point in randomized controlled trials. Std: standard deviation, diff: difference, LL: lower limit, UL: upper limit.

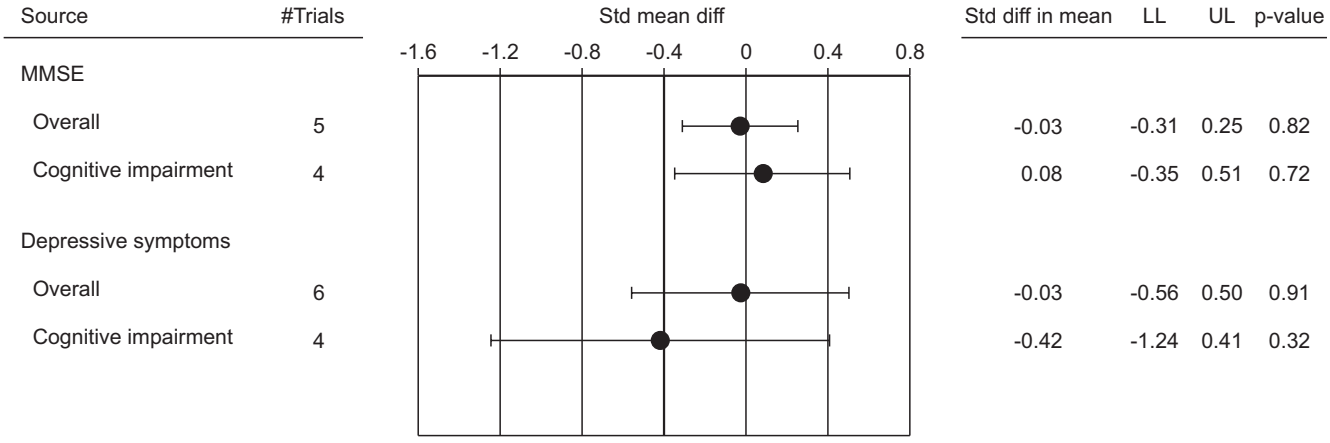

Fig. 2. Weighted standardized mean diff (with 95% confidence interval) of Mini-Mental State Examination test (MMSE) and depressive symptoms at end point in randomized controlled trials. Std: standard deviation, diff: difference, LL: lower limit, UL: upper limit.

weeks. These trials differ in basal TT levels and type of T preparation used (Table 4). In addition, nine were performed in aging men without memory problems, five in subjects with mild to moderate cognitive impairment and two in patients with Alzheimer's disease (Table 4). Since the classification of tests into cognitive domains differed among the included studies, the available neuropsychological tests were divided into seven cognitive domains, based on an established neuropsychological reference text [68], as previously reported (Supplementary Table 1) [32]. In order to obtain more comparable results, only trials with homogenous cognitive tests were analyzed. Combining the results of those trials, when TRT was compared to placebo, no difference in all the cognitive domains analyzed was observed (Fig. 1, Supplementary Fig. 1). In addition, no differences were also observed when depressive symptoms or score derived from Mini-Mental State Examination test were considered (Fig. 2). Similarly, no differences were observed when only patients with cognitive impairment were considered (Fig. 1, 2, Supplementary Fig. 2).

Another recent meta-analysis, including a lower number of RCTs (n=14) and of patients (n=1,406), reported that TRT improved psychomotor speed and executive function. However, the same authors recognized that the effect size was very low, although statistically significant [69].

CONCLUSIONS

Limited preclinical and clinical evidence suggests that T can be involved in the pathogenesis of the age-dependent impairment of cognitive functions. However, when T was evaluated with the gold standard method for sex steroid evaluation (*i.e.*, mass spectrometry) no association between age-dependent reduction of T and memory problems was observed. In addition, the present meta-analysis does not support the use of TRT for the improvement of several cognitive domains analyzed. It is important to recognize that the vast majority of available RCTs included mixed populations of subjects with eugonadism and hypogonadism preventing any final conclusion to be drawn on these issues. In fact, positive effects of TRT were observed either on sexual function [70,71] or on body composition [72,73] only when baseline T levels were below 12 nM. Hence, further larger RCTs are advisable in order to better clarify the role of TRT in aging men, and in particular, in those with a cognitive impairment.

Conflicts of Interest

The authors have nothing to disclose.

Author Contribution

Conceptualization: GC, MM. Data curation: GC, GR, FG. Formal analysis: GC, FG. Funding acquisition: none. Investigation: GC. Methodology: GC. Project administration: GC. Resources: GC, FG. Software: GC. Supervision: GC, AS, MM. Validation: GC, MM. Visualization: GC, MM. Writing – original draft: GC, FG. Writing – review & editing: GC, FG, GR, AS, MM.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.200017.

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