SEXUAL MEDICINE REVIEWS

Is Testosterone a Food for the Brain?

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ABSTRACT

Introduction: Testosterone is fundamental for psychological, sexological, cognitive, and reproductive aspects, and its lack or reduction largely impacts the quality of life in males and females.

Aim: Therefore, the aim of this review is to describe the role of testosterone in the neurophysiology of the brain and related aspects regarding the quality of general and sexual life.

Methods: We listed and discussed the principal studies on the role of testosterone in the brain regarding sexual health, psychopathological conditions, and the elderly. The search strategies were composed by the insertion of specific terms in PubMed regarding the main studies from January 2000 to June 2015.

Main outcome measures: Using a psychoneuroendocrinologic perspective, we considered 4 main sections: brain and testosterone, sexuality and testosterone, psychopathology and testosterone, and cognitive impairment and testosterone.

Results: Much evidence on the neuroendocrinology of testosterone regarding brain activity, sexual function, psychological health, and senescence was found. In any case, it is known that testosterone deficiency negatively impacts quality of life, first, but not exclusively, through a central effect. Moreover, testosterone and androgen receptors are differently expressed according to age and gender. This aspect contributes to gender differences and to the dimorphic physiological role of this hormone.

Conclusion: A universal role for testosterone can be recognized: low levels of testosterone are associated with mental disorders, sexual dysfunction, and cognitive impairment in both sexes. Hence, physicians should carefully assess testosterone levels, not only in the management of sexual dysfunctions but also when seeking to help patients with severe mental or organic diseases.

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Key Words: Testosterone; Testosterone Replacement Therapy; Brain; Sexuality; Psychopathology; Elderly

INTRODUCTION

The secretion of testosterone depends on neuroendocrinologic mechanisms controlled by the hypothalamic-pituitary-gonadal crosswalk. Neurons in the preoptic area of the hypothalamus secrete gonadotropin-releasing hormone (GnRH), which stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the anterior pituitary. LH stimulates the Leydig cells in the testes to produce testosterone and FSH acts on the Sertoli cells to stimulate spermatogenesis. The testes are the main site for the secretion of testosterone during the arc of life, with significant changes in puberty and in senescence. In women, androgen production is due to the activities of the ovary with theca cells, the adrenal gland, and peripheral tissue. The first action of testosterone is during the prenatal phase in inducing sex differentiation, the development of the penis, testes, and male genital apparatus and several aspects of sexual imprinting.[1]

Animal studies have demonstrated that androgen receptor expression is region specific in the cerebral cortex and coupled with significant cellular changes in brain structures.[2] Double labeling immunocytochemical studies for androgen receptors and for neuron-specific markers showed that the majority of receptor-bearing cortical cells are pyramidal neurons.[3]

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On the other hand, cerebral areas in humans, such as the amygdala and hypothalamus, are also strongly testosterone dependent but with significant gender differences.[4]

On the whole, it is also known from pathological conditions that testosterone is fundamental for psychological, sexological, relational, cognitive, and reproductive aspects, and its lack or reduction largely impacts several aspects of behavior. In fact, low testosterone levels induce several symptoms, such as reduced sexual desire, erectile dysfunction (ED), female sexual dysfunction, decreased memory and energy, and poor concentration.[5]

Hypogonadism is a major cause of hypoactive sexual desire disorder (HSDD) and the related decrease in sexual activity that can generate primary and secondary sexual dysfunctions with a worsening quality of life.[6–8]

Moreover, much evidence points to the role of testosterone in mental health, and in this case it is known that in severe forms of psychiatric disease, such as psychosis and mood disorders, there is a significant involvement of testosterone. In some cases, a deficiency of testosterone may exacerbate and worsen psychiatric symptoms.[9]

The decline of testosterone with age is one of the characteristics of most hypogonadism (late onset hypogonadism), although both central (hypogonadotropic) and peripheral (hypergonadotropic) hypogonadism also can be congenital or can occur in young individuals.[10–12]

The decrease in testosterone related to age is one of the main causes of cognitive decline in aging.[13] For this reason, knowledge of the role of testosterone in particular aspects related to neurophysiology, sexuality, psychology, and aging is fundamental in elucidating the link between this hormone and quality of life.[14] In fact, the benefits of replacement testosterone therapy are currently being debated within the scientific community, particularly its impact in senescence, which can improve various physiological functions worsened by a decrease in androgens.

On the whole, testosterone has an important role in the psychophysiology of the brain, and many cognitive, emotional, and biobehavioral functions are dependent on its influence.

Hence, we aim to review the current literature on the relationship between testosterone and the above described aspects from a psychoneuroendocrinologic perspective.

METHODS

Search Strategies

The main methodology used in this review consisted of a careful analysis of literature focused on the role of testosterone in the neurophysiology of the brain.

Therefore, we considered the main original studies and review articles regarding the link between testosterone and the brain in different conditions, normal and pathological.

A computerized search was performed to identify all relevant studies in PubMed from January 2000 to June 2015. The following search terms were used in PubMed: "testosterone and brain," "deficiency of testosterone," "hypogonadism," "testosterone and sexual dysfunctions," "testosterone deficiency and cognitive impairment," "testosterone and psychopathology," and "testosterone and quality of life." Each of these search terms produced a list of many significant studies that we selected on the basis of year of publication (older studies were excluded) in accordance with our aims and the clinical interest for the reader (Table 1).

Brain and Testosterone

The role of testosterone in the brain impacts many psychoneuroendocrinologic, mostly dymorphic, functions: reproduction, sexuality, and cognitive and psychological aspects under the control of several areas, such as the amygdala, the bed nucleus of the stria terminalis (BNST), and the hippocampus. Moreover, testosterone regulates stress responses. In fact, this hormone inhibits activity of the hypothalamic-pituitary-adrenal axis (HPA), the main player in the psychosomatic response to stress.[9]

Studies on animal models verified that the amygdala is an area with a higher density of androgen receptors, and these hormonal receptors play a critical role in the development and maintenance of structural sex differences into adulthood.[15] In humans, functional magnetic resonance imaging (fMRI) studies show that the amygdala activates differently in males and females and much evidence points to a preference for visual sexual stimuli (VSS) in men, whereas women prefer a greater variety of stimuli.[16] Age-related changes in cortical thickness have also been observed during adolescence, with differences between the sexes in hormone-related parts of the brain. For example, the volumes of the medial temporal lobe structures were more pronounced in the later stages of puberty, during which increases in volume were observed in boys but not girls. In addition, global measures for cortical gray matter volume reductions in the later stages of puberty were more prominent in girls than boys.[17] In another study, sex differences were found in associations between circulating testosterone and the thickness of other regions known to have a high density of androgen receptors.[18] All other regions were impacted more by testosterone levels in girls than in boys. This evidence supports 2 hypotheses: (1) testosterone levels directly impact changes in human brain structure, and (2) the regional pattern of sex-by-testosterone interactions would have implications for understanding mental disorders in hypogonadal men.[18] In this regard, the gender differences in the expression of the androgen receptors in the brain drive sexual behavior, and the hypogonadal condition in men mostly impacts cerebral function. In hypogonadal men, there is a significant decrease in many cognitive functions, such as episodic memory, working memory, processing speed, visual spatial processing, and executive function, which are regulated by the androgen receptor-regulated regions of the brain.[19,20] In these cases, age is the main mediator in the relationship between the neuropsychology of the brain and testosterone levels. Hence, low testosterone levels affect cognition and all conditions typified by low testosterone levels,

Table 1. Main Experimental Studies Considered on the Relationship Between Testosterone and Brain

Authors	Study Design	Sample	Main Findings
Psychoneuroendocrinology			
Nunez JL, et al (2003)[2]	Animal models	n = 10 (Sprague-Dawley rats)	Androgen receptors may directly influence the cerebral cortex
Kritzer M (2004)[3]	Animal models	n = 10 (Sprague-Dawley rats)	Pyramidal neurons and androgen receptors play a role in cortical information processing
Schattmann L, Sherwin BB (2007)[22]	Case-control	n = 51	↑T in women, may be associated with poorer performance on cognitive tasks
Barry JA, et al (2013)[23]	Cross-sectional	n = 110	↑T in polycystic ovarian syndrome increases visual spatial skills
Davis SR, et al (2014)[25]	Open-label study	n = 9	Testosterone therapy facilitates preservation of cognitive function
Nguyen TV (2010)[26]	Cell cultures	N. A.	Androgens have a neuroprotective action
Marazziti D, Canale D (2004)[47]	Longitudinal	n = 48	During the process of falling in love, testosterone increases in female and decreases in male
Meydan S, et al (2010)[27]	Animal models	Wistar rats	Testosterone suppresses orchiectomy-induced oxidative damage and morphological changes in the hippocampal tissue
Redoute J, et al (2005)[29]	Case-control	n = 17	↑T increases activation in right insula, claustrum and orbital frontal cortex
Wainwright SR (2011)[63]	Animal models	Adult male Sprague-Dawley rats	Testosterone confers resiliency to chronic stress in males toward affective disorders
Sexual medicine and gender issues			
Hamann S (2004)[4]	Neuroimaging of human neurophysiology	n = 28	The amygdala and hypothalamus are both testosterone-dependent, with significant gender difference
Corona G (2013)[7]	Retrospective	n = 3714	↓T is a clear risk factor for secondary reduced libido
Corona G (2013)[28]	Longitudinal/Cross-sectional	n = 1687	Sexual activity appears to be a protective factor against cardiovascular events
Corona G (2010)[44]	Cross-sectional	n = 2652	Testosterone is involved in ejaculatory control, and cases of premature or delayed ejaculation also are moderated from testosterone levels
Bramen JE, et al (2011)[17]	Cross-sectional	n = 80	Testosterone facilitates a different development in the male and female hippocampus, amygdala, and cortical gray matter
Bramen JE, et al (2012)[18]	Cross-sectional	n = 85	Testosterone impacts on cortical thickness according to gender
Aydogan U, et al (2012)[62]	Longitudinal	n = 79	Testosterone replacement treatment improves psychological and sexological health
Burkhardt MS, et al (2006)[20]	Cross-sectional	n = 45	↑T was not associated with better cognitive function in men at increased risk for Alzheimer's disease
Psychopathology and epidemiology			
Akhondzadeh S, et al (2006)[52]	Cross-sectional	n = 79	↑T decreases severity of negative symptoms
Vercammen A, et al (2013)[53]	Case-control	n = 40	↑T may be of cognitive benefit to men with schizophrenia
Baron-Cohen S, et al (2015)[60]	Retrospective	n = 128	↑T during the fetal period, characterizes males who later receive a diagnosis of autism
Wu F, et al (2010)[10]	Randomized	n = 3.369	↓T is correlated and specified also by a lack of sexual desire and erectile dysfunction
Morsink LF, et al (2007)[65]	Retrospective	n = 2.855	↓T is associated with high rate of depression in elderly
Travison TG (2007)[11]	Prospective cohort	n = 1.532	↓T is not associated to specific lifestyles, such as smoking or obesity
Rausch J (2015)[56]	Case-control	n = 102	↑T is associated with borderline personality disorder, above all in males
Roepke S (2010)[57]	Case-control	n =61	↑T in women with polycystic ovaries is associated with borderline personality disorder
Peters S (2015)[58]	Cross-sectional	n = 173	↑T in boys is associated with reduced amygdala-orbitofrontal cortex connectivity, which in turn is associated with increased alcohol intake

(continued)

Table 1. Continued

Authors	Study Design	Sample	Main Findings
Ramanathan S (2015)[54]	Retrospective	n = 58	↓T in the late onset of puberty, is associated with negative symptoms of schizophrenia
Beyazyuz M (2014)[55]	Case-control	n = 84	↑T is negatively associated with positive symptoms in first episode psychosis
Senescence			
Moffat SD, et al (2002)[13]	Longitudinal	n = 407	↑T was associated with better scores on specific domains of cognitive performance in older men
Brant LJ, et al (2005)[76]	Longitudinal	n = 1.236	↓T was considered a predictor of dementia and negatively impacts cognitive performance
Salminen EK, et al (2005)[78]	Longitudinal	n = 23	↓T due to androgen ablation therapy, is responsible for a deterioration in cognitive functioning
Bussiere JR, et al (2005)[79]	Case-control	N.A.	↓ plays a role in hippocampus-mediated memory processes
Beer TM, et al (2006)[80]	Longitudinal	n = 36	↓T has negative effects on specific cognitive processes in older men
Verdile G, et al (2014)[82]	Prospective cohort	n = 427	Testosterone and luteinizing hormone are involved in the early preclinical stages of Alzheimer's disease
Feldman HA, et al (2002)[83]	Longitudinal	n = 1.079	Testosterone levels are not related to cognition
Hall JR, et al (2015)[84]	Longitudinal	n = 87	The subjects with AD, having borderline or normal testosterone levels, are more subject to development of neuropsychiatric symptoms

Findings have been categorized as directly correlating testosterone and psychoneurendocrine functions, sexuality, and psychopathologies.
↑T = high testosterone; ↓T = low testosterone.

such as hypogonadism, may be detrimental to cognition (Table 2).[21]

In contrast, but interestingly, a particular and controversial situation affects women with polycystic ovary syndrome (POCS), who show higher levels of testosterone with related cognitive alterations in cognitive tasks. However, the role of androgens in these female patients remains unclear, and the cost-benefit of higher levels of testosterone in the cognitive functions is an open discussion.[22,23]

Moreover, this aspect induces us to discuss possible gender differences in women with high testosterone levels compared with men. In women, high testosterone improves abilities in mental rotation tasks, while in men low testosterone is associated with better spatial abilities.[24]

On the other hand, testosterone therapy is associated with reduced blood oxygen level-dependent signal activation in key anatomical areas during fMRI verbal fluency and visuospatial tasks in postmenopausal women. This evidence suggests that testosterone therapy facilitates the preservation of cognitive function in both sexes.[25]

Finally, an important effect of testosterone concerns cellular neuroprotection through specific mechanisms that protect against apoptosis, above all in hippocampal regions[26,27] (Table 1).

Testosterone and Male/Female Sexual Function

Sexual activity increases the level of testosterone and improves quality of life,[6,28] with a positive influence on brain activity. There is evidence of a link between testosterone, brain activity, and sexual behavior. For example, it has been demonstrated that VSS differ among eugonadal and hypogonadal men, with the latter showing a decreased activation of the right insula, clastrum, and orbitofrontal cortex (OFC), regions implicated during sexual arousal in men with normal levels of testosterone.[29] Actually, many studies demonstrated a strong association between testosterone and sexual function. A famous case report in *Nature* >40 years ago first discovered the link between sexual stimuli and beard

Table 2. Pathological Conditions Associated With a Deficiency in Testosterone

	Deficiency in Testosterone
Brain	Alterations in the cerebral differentiations contrasting the chromosomal sex; alterations of cortical thickness
Sexuality	Hypoactive sexual desire disorder, erectile dysfunction, ejaculatory disorders, decrease in sexual activity, hypolubrication, orgasmic disorders
Psychological aspects	Anxiety, depression, schizophrenia, stress response with interaction between HPA and HPG axes
Cognitive aspects	Reduction of episodic memory, working memory, processing speed, visual spatial processing, executive function

growth, which is a typical testosterone-dependent function.[30] Moreover, animal models have shown that sexually naïve males exposed to a sexually receptive female increase LH and testosterone secretions.[31] In humans, other investigations have highlighted the link between ED and testosterone,[32] sexual arousal, and LH pulsatile secretion,[33] sexual activity and testosterone production,[34,35] and, in an indirect manner, the resumption of sexual activity after treatments with the type 5 phosphodiesterase inhibitors for the treatment of impotence also contributes to increased testosterone levels.[36] The testosterone level in the low to low-normal range in subjects lacking sexual activity has been named subclinical hypogonadism (ie, a "condition of impotent patients with psychosomatically reduced— with respect to normal controls—T and increased LH").[37]

Moreover, a recent meta-analysis clarified that in men with clear hypogonadism, testosterone replacement therapy improves sexual health.[38] Hence, there is much evidence to suggest that sex and testosterone production have a mutual influence. A recent article has specifically discussed the influence of testosterone in men with impotence, suggesting in selected cases combined therapy with PDE5 inhibitors, and, above all, the evaluation of testosterone in men suffering from erectile dysfunction.[39]

From this evidence, it appears clear that sexual activity boosts testosterone production, which will stimulate desire and future sexual activity: this is the virtuous circle that, in pathological conditions, such as ED for any cause, can be transformed into a vicious circle.[6,36]

A study using fMRI demonstrated that VSS activate the inferior temporal cortex, the right insula, the right inferior frontal cortex, and the left anterior cingulate cortex, which are positively correlated with plasma testosterone levels.[40] Similar findings have been obtained noninvasively through the evaluation of salivary testosterone.[41] Testosterone is largely implicated in the different phases of erection.[42] In fact, changes in testosterone levels from the flaccid state to tumescence and erection differ between men with or without ED.[43] On the other hand, the hormonal system also is involved in ejaculatory control, and also in this case testosterone has an indipendent role together to prolactin and thyrotropin.[44]

In the same manner, testosterone also plays a key role in women and low levels have been associated with a decrease of libido and sexual pleasure, orgasmic dysfunction and hypolubrication. In this regard, studies have shown that therapies with testosterone directly improve sexual function both in pre- and postmenopausal women.[45]

In conclusion, it seems clear that the sexual activity can raise levels of testosterone (within the normal range), and the lack of sexual activity is correlated to lower testosterone levels with respect to controls with normal sexual activity. In contrast, the resumption of sexuality in successfully treated impotent patients, irrespective of the nature of treatment, restores testosterone to levels comparable to controls[46] (Figure 1).

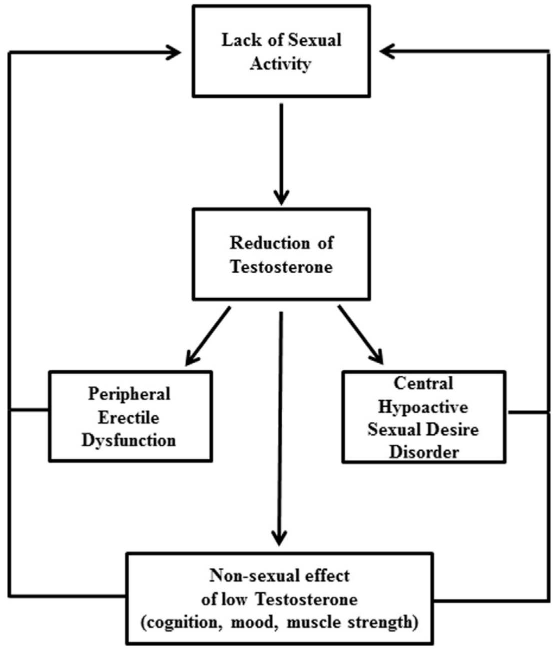

Figure 1. The vicious circle correlating with the lack of sexual activity, irrespective of causes, and the sexual symptom—erectile dysfunction (ED) and hypoactive sexual desire disorder (HSDD)—related to the relative reduction in testosterone level (subclinical hypogonadism). This situation could be further amplified by the physical and behavioral testosterone-related symptoms.

Assuming that sexual activity increases testosterone production, what is the role of androgens in the ability to fall in love? Testosterone facilitates rapprochement of the sexes when a man and a woman fall in love (Table 1), with higher levels found in women and lower in men compared with single people or those in a long-term relationship. These differences, as with other hormonal patterns, disappear between 12 and 24 months later, during the latter phase of falling in love.[47] In conditions of love, the central control for the emotional response plays a fundamental role with the involvement of the neuroendocrinologic and the cognitive regions from the hippocampus, amygdala, hypothalamus, nucleus accumbens, and anterior cingulate cortex.[48]

In this regard, another interesting issue concerns the relational status, marriage, fatherhood and motherhood, and the level of testosterone in males and females. These life conditions have a different specificity for androgen physiology: in women, for example, testosterone decreases during marriage and motherhood.[49] In males, on the other hand, testosterone increases before the phase of mating and decreases during marriage and fatherhood.[50]

Testosterone and Major Psychopathologies

Hormones play an important role in several mental disorders and many clinical studies have investigated the relationship between psychopathologic and endocrine aspects. In fact, several hormones and their receptors have been found to be involved in severe mental disorders.[51]

Some studies suggest that a dysfunction of the HPA and/or the HPG axis might contribute to the pathophysiology of schizophrenia. In particular, an inverse correlation between testosterone and the negative symptoms assessed with the Positive and Negative Symptoms Scale were found in chronic psychotic patients.[52] Another investigation with neuroimaging analysis revealed that men with schizophrenia show a less pronounced increase in activation when inhibiting responses to negative stimuli; however, they did show a strong inverse association between serum testosterone levels and activation of the bilateral middle frontal gyrus. Hence, endogenous testosterone levels may play an enhanced modulator role in determining the neural and behavioral response during cognitive-emotional processing in schizophrenia.[53]

The relationship between testosterone and psychosis also was recently investigated in a retrospective study on a sample of schizophrenic patients and their families focused on at the age of puberty. Male subjects with a delayed onset of puberty showed an elevated association with negative prodromal symptoms of schizophrenia, highlighting the possible predictive role of male steroids during puberty in the exacerbation of psychosis,[54] above all for negative symptoms such as apathy, avolition, anhedonia, and asociality, whereas positive symptoms have been found recently to have a reverse association with testosterone in a sample of first-episode psychosis patients.[55] In personality disorders, the hormonal system also is involved in the clinical manifestation of these mental diseases, and in borderline personality disorder (BPD) in particular, the increase of testosterone causes relational difficulties.[56,57]

Moreover, an important concern surrounds the use of alcohol in adolescents as a deviant conduct that could depend on the interaction between the amygdala, OFC, and testosterone. Amygdala is an area with a high density of androgen receptors and high levels of testosterone seem to modify the connectivity between amygdala and OFC, with a major risk of increased alcohol use.[58]

A recent study noted that hormonal dysregulation in mothers is involved in the pathogenesis of autism.[59] In this regard, some evidence showed that an alteration and an increase in fetal testosterone in the prenatal phase could have an impact on the correct development of the child with a possible exacerbation of an autistic spectrum disorder.[60] Moreover, interesting research revealed that during puberty, the levels of circulating testosterone are inversely associated with the risk of eating disorders in males, highlighting the influence of possible psychobiological patterns regulating disordered eating behavior in boys.[61]

In this regard, the gender issue was extensively examined in a recent review of the role of testosterone in anxiety and depression and the major prevalence of these mental diseases in women. Testosterone is the responsible of gender difference linked to mental health, also considering the different female hormonal conditions associated with anxiety and mood disorders.

Testosterone is seen once again as a protector against anxiety and depression in males, and many studies have confirmed this. The amygdala, the bed nucleus of the BNST, and the hippocampus are the main central areas with a high sensitivity to changes in testosterone levels. Therefore, this link and the expression of testosterone in the brain have a direct effect on mental health and represent the future of scientific knowledge on its psychoendocrinologic role.[9]

Moreover, young patients with congenital hypogonadotropic hypogonadism have a high incidence of sexual dysfunction, anxiety, and depression and a poorer quality of life, suggesting that low endogenous levels of testosterone are associated with the increased incidence of psychological symptoms.[24] In these cases, testosterone replacement therapy improves not only sexual function but also mental health and quality of life.[62] In another study involving animal models, the effects of gonadectomy are described. The authors found that testicular hormones protect the animals from depressive behaviors and alterations in neurogenesis and neuroplasticity following chronic mild stress,[63] although in another study on mice, testosterone also is seen to have an anxiolytic effect.[64] On the other hand, in a large study on an elderly population, it has been observed that low levels of the weak adrenal androgen dehydroepiandrosterone (DHEA) are associated with higher depressive symptoms in both men and women[65]; however, other recent findings and the current guidelines showed that DHEA therapy is not effective for mood disorders and depressive symptoms in men.[66,67]

Hence, much evidence shows that decreased levels of testosterone are associated with depression and anxiety[9] and that testosterone undecanoate administration can improve depressive symptoms,[68] above all in hypogonadal men with sexual dysfunctions, although other psychoneurological factors also are involved in mood disorders (Figure 2).

From a therapeutic point of view, the positive effects of testosterone on depressive symptoms start to take effect as early as 3 to 6 weeks later, but it will most likely take 18 to 30 weeks for the patient to experience significant improvement.[69] On the basis of a case-control study with testosterone replacement therapy, it has been hypothesized that, in depression, the receptiveness to testosterone effects depends on dysregulation of noradrenaline and serotonin and on baseline testosterone concentrations.[70] Finally, another experimental study on patient groups treated with placebo, testosterone, or finasteride revealed that testosterone positively acts on depressive symptoms and moderately increases the spatial memory. However, in this case, the cost-benefit ratio related to finasteride, which along with dutasteride, may have a number of sexual side effects,[71] is at least controversial (Table 1, Figure 3).

Testosterone Deficiency and Cognitive Impairment

Several mechanisms, such as hormonal changes, are involved in the cognitive deterioration characteristic of aging. In this regard, the conceptualization of the brain as a "multidisciplinary

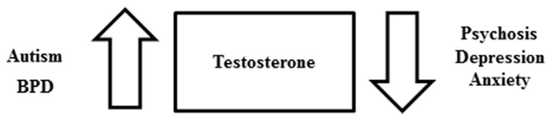

Figure 2. The levels of testosterone impact differently on mental disorders. The prenatal exposure to androgens and testosterone represents a risk factor for autism. On the contrary, in psychosis, depression and anxiety, testosterone has many benefits. BPD = borderline personality disorder.

organ" conceived to regulate both cognitive functions and the production of hormones, and to be itself a target of steroid and sex hormones,[72] might be useful in comprehending the connection between it and the complex hormonal system.

Male and female sex hormones play a different role in cognitive functions. If data regarding the neuroprotective effect of estrogens on the hippocampus of aging women are relatively clear,[73] the role of testosterone relative to cognition appears still to be controversial. A review article discussed the role of a decrease of testosterone in the hippocampus in animal studies, observing the importance of androgens in this cerebral area for memory tasks.[74]

Some researchers have shown an association between a decrease in total testosterone levels and the onset of cognitive decline (ie, vascular dementia, Alzheimer's disease [AD]).[13] Similarly, it has been suggested that a decline in testosterone levels at the rate of 1% per year may be considered a possible risk factor for mild cognitive impairment, as well for AD.[75] The possible protective effect of testosterone on brain activity is founded on the comparison of testosterone levels in healthy elderly men with those of patients of the same age but with mild cognitive impairment or with moderate to severe AD. Levels of testosterone but not estradiol, were significantly lower in the group of men affected by AD.[13] In addition, data from the Baltimore Longitudinal Study of Aging[76] revealed the potential of low testosterone levels to predict cognitive disorders, such as dementia, prior to their onset. In particular, this study aimed to investigate cognitive performance, together with total serum testosterone and the free testosterone index, of a sample of 1,236 subjects not affected at the beginning of the study by any kind of dementia. The cognitive functioning and testosterone levels were monitored during several follow-ups. In the following 20 years after starting data collection, 9% of participants (114/1236) developed AD. The authors have highlighted, with a retrospective analysis, that cognitive performance and testosterone levels can predict AD onset. Specifically, a low free testosterone index and difficulties in visual memory tasks were associated with an increased risk of developing AD.

In support of these findings also are data regarding the cognitive functioning of hypogonadal men, or men affected by prostate cancer. These studies revealed, although not always in a unequivocal way, that low testosterone levels, both due to hypogonadism[77] and due to androgen ablation therapy,[79,80] are responsible for a deterioration in cognitive functioning. Hence, hypogonadism or androgen deprivation is more associated with a cognitive decline than mere aging. This supposition is supported by another study[73] that showed that, unlike elderly hypogonadal men, elderly men with higher levels of free testosterone had better performance in some kinds of cognitive tasks.

Although several studies have found an association between low testosterone levels and an increased risk of developing AD,[81,82] there are conflicting data about the role of testosterone in cognitive functioning. In fact, some reports failed to

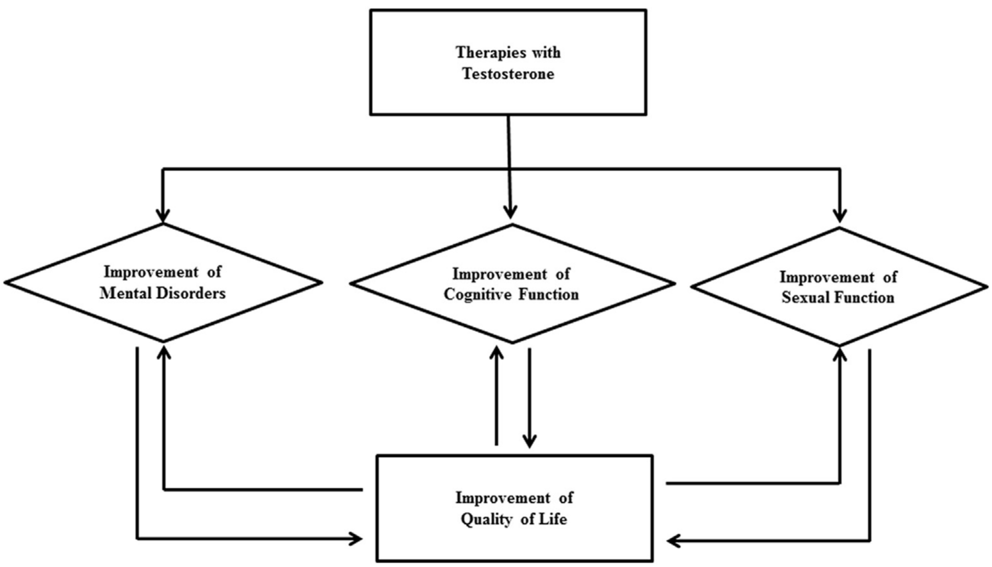

Figure 3. Therapies with testosterone can be useful for many pathological conditions related to mental health, sexuality, and cognitive function. In many cases, exogenous testosterone per se or in combination with other drugs improves quality of life.

demonstrate the observational correlation between circulating levels of androgens and cognitive functioning. Among them, Feldman et al did not find any evidence of a correlation between serum levels of testosterone and cognition.[83] In addition, more recently a study has demonstrated that elderly subjects with AD but with borderline or normal testosterone levels are more likely to develop neuropsychiatric symptoms, such as hallucinations, delusions, and irritability than AD subjects with low testosterone levels.[84] Hence, higher levels of testosterone, which are known to downregulate the interaction between the cognitive and emotional systems, could decrease the cognitive control, resulting in behavioral problems.

Based on these findings in the literature, the measurement of testosterone levels in subjects at risk of developing a cognitive impairment such as AD might be considered an early screening for the primary prevention of AD. However, the use of testosterone replacement therapy as a protective agent against cognitive impairment should be considered cautiously. More scientific evidence is necessary to confirm or reject the beneficial effect of testosterone in preventing cognitive impairments (Table 1).

CONCLUSION

There is much evidence to suggest that testosterone greatly contributes to quality of life throughout life (Table 2, Figure 3). Reviewing current literature, we found that testosterone plays a pivotal role, not only in brain function and sexuality but also in psychological health and cognitive performance. Although highlighting the role of a single factor involved in so many processes in such a grand manner could appear to be a epistemological risk in this modern era of medicine, the deficiency of this hormone, as in hypogonadism, is certainly a significant risk factor for general health and many medical disciplines have been called on to consider the fundamental role of testosterone in human psychophysiology.

Hence, physicians and health operators should carefully assess testosterone levels in patients with problems in these discussed areas, In this regard, hormonal therapy is often suitable for a range of pathologic conditions that involve mental health, sexuality, and cognition, including age-related cognitive function.

A holistic perspective is the frontier and the main challenge for the health care system in order to guarantee adequate treatment for patients with psychoneuroendocrine diseases.

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