Review Article
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Testosterone and brain aging

Abstract

Testosterone is an essential hormone to maintain brain health and function. It also exerts a specific activity on the peripheral nervous system, maintaining skeletal muscle activity. The brain has a wide distribution of androgen receptors (AR) in the cortical area, hippocampus, hypothalamus, telencephalon, and amygdala. AR is also in the brainstem and spinal cord areas associated with sensory functions and in Purkinje cells of the cerebellar cortex. ARs were found on axons and dendrites, evidencing extranuclear activity. Testosterone regulates neuronal growth, differentiation, survival, or death through both genomic and nongenomic signaling pathways. Testosterone is metabolized in other hormones: in DHT acting on the hippocampus and 17β-estradiol, which explicitly affects dendritic arborization in females and males. Furthermore, testosterone stimulates oligodendrocytes and myelin formation, while estrogens stimulate mitochondrial activity, anti-inflammatory effect, and astrocytes protection.

Testosterone improves the survival of human neurons and astrocytes, acting directly on the mitochondrial membrane and inhibiting the reactive oxygen species. Furthermore, it exerts a protective effect on brain function, preventing Alzheimer's disease, reducing the formation of amyloid β(Aβ) peptides in cortical neurons, and neurotoxicity. Furthermore, testosterone is an effective therapy to restore hippocampal function and related pathology, increasing adult neurogenesis within the dentate gyrus region of the hippocampus through an androgen-dependent pathway. Testosterone stimulates myelin regeneration, representing the primary therapeutic goal in demyelinating diseases. There is evidence that it can be effective in various neurodegenerative diseases, such as Parkinson', SLA, and multiple sclerosis (MS). In this review, the effect of testosterone on neurons, demyelinating diseases, muscle strength loss, mood, and depression have been investigated.

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Introduction

Testosterone is the primary androgen secreted by Leydig cells in men and ovaries in women at lower quantities. Testosterone is essential in the development of sexual characteristics in men and in maintaining the function of tissue in both sexes for all life, such as muscular development, strength, cardiac and brain function, body air, and sexual activity. Testosterone plasma levels in men decrease with progressive age,[1] and in older men as aged≥70 years, a significant reduction is observed. In me, at the age of 60 years, low testosterone levels were found. However, testosterone replacement therapy remains a topic of debate due to potential adverse effects, including cardiovascular risks and increased hematocrit levels, which require careful consideration. In the elderly, reductions in muscular strength and unfavorable body fat distribution due to low testosterone levels were observed.[2] Low testosterone was associated with tiredness and fatigue. Nowadays, among middle-aged and older, the administration of testosterone is considered an anti-aging strategy.[3] This article aims to evaluate the effect of testosterone on the central and peripheral nervous system. However, testosterone therapy may cause some adverse effects; in particular, its impact on cardiovascular events and mortality and the increase in hematocrit and hemoglobin levels should be considered. In contrast, physiological replacement therapy may improve physical function, mental wellness, and sexual activity density.[4]

Metabolism of testosterone

The effect of testosterone is complex because it acts on the neuron in different manners because it is metabolized in various hormones with distinct activity on tissues. Testosterone is metabolized in dihydrotestosterone (DHT) after the reduction of the 5α-reductase, and in 17β-estradiol after the effect of aromatase.[5] DHT, the most potent androgen, is transformed in androstenedione and in 3α and 3β-diol metabolites, which have estrogenic effects. Testosterone and DHT (but all androgens as DHEAS or synthetic steroids) activate the AR that are widely expressed on neurons and stimulates oligodendrocyte, myelin repair, and axon regeneration.[6] 17β-estradiol and 3α-diol and 3β-diol stimulate mitochondrial function, anti-inflammatory effect, and exerts astrocytes protection.[7] See figure 1 Testosterone also has important metabolic effects: it increases insulin activity, reduces central obesity in obese patients with type 2 diabetes,[8] and reduces metabolic syndrome.[9] Furthermore, many synthetic derivates from testosterone (such as oxandrolone, stanazolol, nandrolone, methenolone, etc.) are the androgen anabolic steroids that activate the AR and ER.

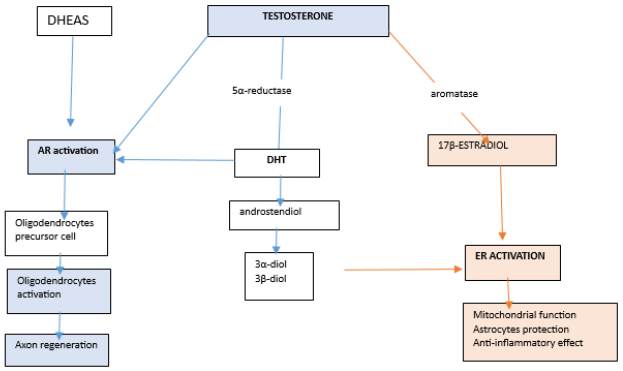

Figure 1 The metabolic way of testosterone. Testosterone, can be transformed in DHT, and 17 β-estradiol DHEAS is produced by adrenal gland. Testosterone, DHT and DHEAS activate AR receptors that simulate oligodendrocyte precursor cells and, consequently, their activation. Oligodendrocytes stimulate myelin formation and axon regeneration. 17 β-estradiol activates the ERs, which increases mitochondrial function, protects the astrocytes, and exerts an anti-inflammatory effect.

Effect of testosterone on the brain

Testosterone and other steroid hormones can cross the blood-brain barrier BBB.[10] The effect of testosterone on the brain is due to the extensive-expression in the brain of AR, which was detected in the cortical area, hippocampus, hypothalamus, telencephalon, and amygdala.[11] ARs are also expressed in the brainstem and spinal cord areas and the cerebellar cortex.[12] Testosterone and its derivatives effectively activate the androgen receptor (AR) on neurons, dendrites, myelin, and astrocytes. Androgens stimulate neuronal growth, differentiation, and death.[13] The loss of AR function could contribute to the development of neurodegenerative diseases.[14,15] ARs were found on axons and dendrites, evidencing extranuclear activity.[16] Figure 2. The brain is an androgen-dependent organ, and its effect its function is largely conditioned throughout life. In the neonatal male, it appears the effect of androgen on the hippocampus and DHT, but not estrogen, exerts a specific effect on dendritic arborization both in females and males[17] that is blocked by AR antagonist.[18] A neuropathological investigation conducted on postmortem patients of 80 years and older showed lower levels of testosterone in the brain correlated with age, while no changes of 17β-estradiol levels in the brain were observed.[19]

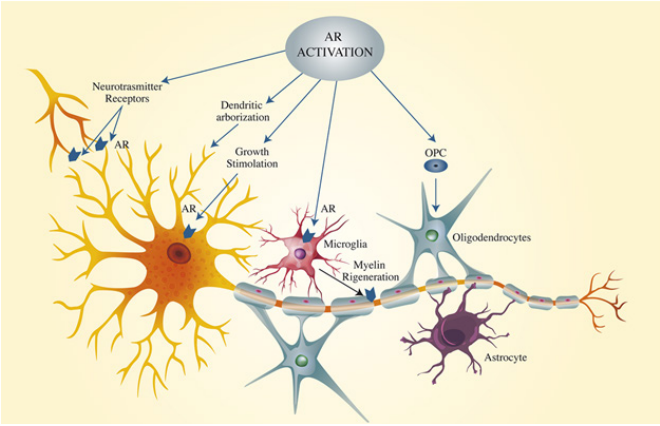

Figure 2 The activation of AR in neurons. The AR distribution is represented. AR are located on the dendrites, on neuron body cell, on oligodendrocytes on microglia. The activation of AR stimulates the neuronal body, dendrites arborization that increase the neural connection, the OPC and microglia that stimulates myelination and axon protection.

In animal models, it was demonstrated that testosterone, through the activation of AR, exerted a protective effect on brain function, preserving Alzheimer's disease.[20,21] In rats, testosterone administration determines an increased secretion of the non-amyloidogenic APP fragment, a reduced formation of Aβ peptides in cortical neurons,[22] and reduced neurotoxicity.[23,24] This process is mediated by the activation of AR and inhibited by flutamide, an androgen receptor antagonist.[21] Testosterone improves the survival of human neurons and astrocytes by stimulating mitochondrial activity and inhibiting reactive oxygen species production,[25,26] reactive nitrogen species (NOS) generation,[27] and SIRT1 expression.[28] These data demonstrate that testosterone is an effective therapy to restore hippocampal function and related pathology.[29] Testosterone enhanced synaptic plasticity in rats, scavenging free radicals and increased the number of intact cells and the dendritic spine density in the hippocampal region.[21] Neurogenesis occurs in adults, but the functional significance remains to be explained. Sex steroids play a fundamental role in adult neurogenesis. In rodents, testosterone stimulates adult neurogenesis within the hippocampus through an AR pathway.[30] The potent regulators effect of androgen on adult neurogenesis in the hippocampus via the AR has also been demonstrated in other than the dentate gyrus.[31] Neuroprotection is induced by androgens through the AR activation independently by estrogens.[32] Androgens increase cell survival in the dentate gyrus, and this process can be blocked by the administration of flutamide, an AR antagonist.[31]

The neuroprotective effect of testosterone on the brain has been proposed as a complementary therapeutic intervention in neurodegenerative disease.[33] Androgens induce neuroprotection through AR activation independently of estrogens.[32] Androgens increase cell survival in the dentate gyrus, and this process can be blocked by the administration of flutamide, an AR antagonist.[31] Myelin regeneration is the essential therapeutic goal in demyelinating diseases.[34] In *Alzheimer's disease* (AD) the regulation of Aβ deposition is regulated by the activation of both AR and ER[35] however, testosterone has a direct neuroprotective effect, independently by its conversion into estradiol.[24,36] 17β-estradiol substantially contributes improving the hippocampal function favouring the cleavage of APP[37] and increasing BDNF secretion.[38] Estradiol inhibits BACE1 expression[39] and induces α-APP secretion by activating the MAPK-signalling pathway independently of ER.[40] Testosterone, methyl testosterone, and 17-beta-estradiol reduced neuronal death by 80-90%, and the anti-Aβ effect of testosterone is potentiated by estrogenic levels.[41]

Testosterone enhanced the synaptic plasticity increasing the number of new cells and the density of dendrites in the hippocampus,[21] and reduced the oxidative stress activating SOD and GSH-Px enzymes.[42] The neurodegenerative process is strongly sustained by oxidative stress[43] and by a deregulation and hypofunction of N-methyl-d-aspartate (NMDA) receptor[44,45] as observed in AD.[46] The protective effect of testosterone on brain function was demonstrated in animal models preserving from AD.[20,21] The proteins in the hippocampus, p-NMDAR1, and p-CaMK II, were correlated with reduced oxidative stress.[42] The main action of testosterone on the brain is the effect against oxidative stress,[26] and reduction in neuronal death by increasing eNOS activity and SIRT1 expression.[28] A low serum testosterone level in men was associated with augmented Aβ deposition in brain tissue, predisposing to the development of AD[47-52] while a high testosterone level reduces the onset and development of AD.[53] Higher free testosterone levels were associated with lower cerebral Aβ deposits in females. In males, free testosterone was positively related to hippocampal volume and significantly interacted with cognitive status.[47,54] Estrogens contribute to the remyelination process in different manners[55] in the clinical evaluation of the effects of testosterone should be considered.

Testosterone therapy in patients with AD

Androgen deprivation therapy (SDT) as observed in patients with prostate cancer (PC) demonstrated that men had a a higher risk of cognitive impairment and dementia[56] and worsening depression[57] confirmed by a recent meta-analysis.[58] HowEver, the effect of testosterone administration as a treatment to improve cognition in patients with AD remains still controversial. Many studies evaluated the effect of testosterone therapy in patients with AD[21,59-74] which are reported in Table 1. Some studies found positive effects of testosterone therapy on some cognitive function in normal and hypogonadal elderly men,[60,62,64,72,75-76] while others had no conclusive results.[61,62] The studies conducted on small groups of patients have the risk of many biases. Firstly, the dose of testosterone administration is the most critical point. The testosterone gel has a lower effect than intramuscular injection. Secondly, the plasma levels of other hormones evaluated (as 17β-estradiol, IGF-1) that significantly contribute to brain functions were not regularly evaluated and sometimes without a strong statistical analysis considering the various confounding factors.

Importantly, not all screening instruments for the early detection of Alzheimer's disease and cognition function are appropriate to be a promising screening test for memory clinic testing for population screening[77] See Table 1.

Table 1 Effect of testosterone therapy on AD and cognitive impairment

Authors	Patients	Age	Study	Therapy	Duration	Outcomes
Resnick, 2017	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, 2016	44 men	≥50 yrs	RCT	T gel 50 mg	24 weeks and 4 weeks washout,	Significant improvement in general cognitive functioning.
Huang, 2016	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, 2015	44, older men	61 ± 7.7	RCT	transdermal T (50 mg/day)	24 weeks	Significant increases in plasma androgens levels. No changes in plasma amyloid-beta. Dementia is not investigated.
Cherrier, 2015	351 men community. 37 with MCI and low T	70.5 ± 8.2	RCT	T gel (50 to 100 mg/day)	3 months	Modest improvement in verbal memory and depression symptoms
Borst, 2014	60 hypogonadal men	70.8	RCT	T-enanthate (125 mg/week)	12 months	Small improvements in depressive symptoms and visuospatial cognition.
Young, 2010	26 young 62 older	25-35 60-80	RCT	GnRH agonist, T-gel T-gel, 75 mg and 100 mg	6 weeks	Free T positively correlated to spatial cognition while estradiol negatively correlated with working memory
Emmelot-vonk,2008	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, 2007	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, 2007	15 normal men	66-87	RCT	T enanthate (200 mg im every other week	3 months	Decreased verbal memory and altered relative activity in medial temporal and prefrontal regions.
Charrier, 2007	57 eugonadal men	67 ±11	RCT	T enanthate i.m. 50, 100 or 300 mg/week	6 weeks	No significant changes in memory.
LU, 2006	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, 2005	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, 2004	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, 2003	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'Connors, 2001	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, 2001	25 healthy men		RCT	T enanthate 100 mg weekly	6 weeks	Short-term T administration enhances cognitive function

RCT, randomized controlled trial; AD, Alzheimer's disease; T, testosterone; MCI, mild cognitive impairment; ADA Scog=Alzheimer's disease Assessment Scale cognitive subscale; MMSE, mini mental status examination; CDT, clock drawing test; RCT, double-blind placebo-controlled study.

Multiple sclerosis

In Multiple sclerosis (MS), which is an autoimmune inflammatory disease of the CNS and is characterized by neuronal demyelination with subsequent axonal dysfunction and paralysis. Testosterone appears to have a specific indication for the treatment of these alterations. Symptoms of MS range from loss of vision to neuromuscular disorders. Testosterone plays a significant role in the incidence and progression of MS, with a clear predominance in women.[78] Estrogen and androgen therapy in MS, has shown encouraging results.[79] A study conducted in 10 men with MS with relapse remittent form (RRMS) demonstrated that testosterone exerted a neurotrophic effect on the brain, reducing atrophy and increasing the gray matter in the right frontal cortex. The cortical lesions and brain atrophy are correlated with mental disorders in RRMS.[80] These data are of relevant importance for the clinical outcome of these patients. Still, unfortunately, only a few studies on this area have been conducted.

ALS (amyotrophic lateral sclerosis)

ALS is characterized by the primary degeneration of upper (motor cortical) and lower (brainstem and spinal) motor neurons. Muscular atrophy is the consequence of neuron damage. During autopsy, it was found that lateral sclerosis refers to the lateral white matter of the funiculus in the spinal cord (degeneration of the corticospinal tract).[81] In a mouse model of ALS, it was found that testosterone compacts the myelin sheet.[82,83] Neuronal apoptosis is a complex process that is not yet well understood. Spinal motor neurons degenerate with the reduction of muscle trophic factors, not only when the androgen levels are low but also when the IGF-1 level is significantly low.[84] In animal models and humans it was observed the interactions between androgens and IGF-1.[85] IGF1 sustains and increases the cellular effect of testosterone.

High doses of testosterone have a negative effect on the endothelial function of the aorta and erectile activity.[69] Higher doses of androgen therapy exposure trigger persistent changes in BDNF expression.[86] Supraphysiological exposure to androgens exerts neurotoxic effects, increasing the intrinsic apoptotic pathway and alterations in neurite networks. There is a loss of neurite formation and a reduction of the total length of dendrites. Particularly in neurodegenerative diseases such as Alzheimer, there is the need for more robust clinical evidence. DHT seems more effective in the therapy of ALS because it increases the expression of IGF-1 in muscle, exerting myotrophic and neurotrophic effects. DHT treatment reduces the denervation at the neuromuscular junction and motoneuron loss, ameliorating clinical symptoms in ALS, and can be considered a therapy to improve the clinical outcome.[87] ALS and its psycho-neuro-endocrinological sequelae should become an area of intensive study in the future.[88] Further studies on the effects of androgens in ALS should be explored because they can be of relevant help to the patients.

Effect on muscular strength

The anabolic effect of testosterone is due to increased muscle protein synthesis,[89] stimulating satellite cell replication,[90] inhibiting muscle protein degradation,[91] and increasing neural growth. In elderly men, testosterone administration, after six months of therapy, induced an increase in total lean body mass and muscular strength[92] and maximal voluntary strength in a dose-dependent manner but no effect on endurance.[93] In aging, sarcopenia is due to fiber and mitochondrial dysfunction. Sarcopenia is associated with loss of muscular strength, physical disability, and reduced quality of life. The nervous tissue change is substantially involved in the lives of elderly people, and the type 2 fast fibers preferentially undergo denervation. In the recovery process of these patients, reinnervation of the musculature is essential.[94] In aging sarcopenia, denervation and muscle fiber atrophy are associated and characterized by motor unit loss and skeletal muscle alterations.[95] Physical exercise at high intensity stimulates muscle reinnervation in the elderly.[96] The association of androgen therapy significantly increases the neurodegenerative process in the skeletal muscles.[33] The neuroregenerative process has also been observed in a Charcot-Marie-tooth patient after oxandrolone treatment for three months.[97]

Connor et al.,[98] in a randomized, double-blind, placebo-controlled, crossover study, showed that testosterone associated with exercise compared to the exercise-placebo group for 12 weeks, with a two-week wash-out, significantly increased muscle strength and physical function. Testosterone treatment to reach physiological plasma concentrations in middle-aged and older men can improve lean body mass, whilst exercise training enhances muscular strength.[99] particularly in neurodegenerative diseases such as Alzheimer, highlighting the need for more robust clinical evidence.

Effect on mood disorders and depression

In elderly men with a decline in testosterone levels, the incidence of depression increases[100] it also occurs in young men.[83] The Endocrine Society Clinical Practice Guideline established hypogonadism criteria requiring two-morning serum testosterone levels below 280–300 ng/dl (9.7–10.4 nmol/L SI units).[84] Testosterone is a neuroactive steroid hormone[85] because it acts on DOPA receptors. Men with an average age of 64.5 years who have a total testosterone below 200 ng/dl (6.93 nmol/L SI units) compared to eugonadal men had a higher incidence of depressive disorders.[101] In the Rancho Bernardo Study, it was found a significant association between increasing severity of major depressive disorder and low circulating levels of total testosterone in men.[102] A systematic review with meta-analysis of case-control studies demonstrated that males with depressive disorders had significantly lower plasma testosterone concentrations than healthy controls[103] and, of particular interest, inversely associated with levels of bioavailable and free testosterone and dihydrotestosterone,[102,104] not always considered in clinical trials. Furthermore, the loss of interest in most activities and low physical energy, and psychomotor retardation contribute to physical inactivity and depression.

An association between hypogonadism and depression has been observed. Observational, cross-sectional, or longitudinal studies reported an inverse relationship of depression scores in men with circulating testosterone levels.[105] Men suffering from depression have lower circulating testosterone levels,[102,106-107] and men with hypogonadism can manifest depressive symptoms.[108] Hover Seidman et al.[109] showed that low level of testosterone was more related to dysthimic disorders than depression. Morphologic and functional studies have confirmed the effects of sexual hormones in cerebral regions of interest men have lower circulating testosterone levels.[110,111] Barriere et al.[110] demonstrated significant sex differences in gray matter concentration at the level of the gonadotropic axis, in the hypothalamus and pituitary but also within the hippocampus and the amygdala of intact animals. However, more recent studies evidenced that severe depressive symptoms do not respond to testosterone therapy.[112] Handelsman et al.[113] found that testosterone treatment can have minimal efficacy compared with a placebo, showing reasonable safety for up to 2 years. Generic mood elevation does not necessarily signify treatable depression. Depressed patients showed worse sleep than controls, but no significant difference in endogenous hormone levels was found, but the associations between endogenous sex hormones and depressive symptoms were inconclusive.[114]

The benefits of testosterone replacement therapy in men with major depressive disorder and low testosterone levels in the clinically defined hypogonadal range remain uncertain and require further investigation.[115] For Grossmann et al.[116] testosterone treatment for 2 years in a group of 1007 patients improved the health-related quality of life, better baseline physical function, greater sense of coherence, and fewer depressive symptoms. The mental health benefit was associated with weight and waist circumference reduction, but testosterone did not affect psychological and physical function or depressive symptoms. In men with minor or more depressive symptoms, testosterone treatment was associated with small but significant improvements in mood and energy. Testosterone substitution can positively influence the quality of life in older hypogonadal men, as has been demonstrated in large placebo-controlled trials.[117]

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Depression disorders are a complex clinical condition. The DSM-V (*Diagnostic and Statistical Manual for Psychiatric Diseases*) defined depressive disorders range from dysthymia/minor depression to major depressive disorder[118] is more appropriate for this clinical evaluation. Furthermore, polygenic mechanisms are likely to be critical to the biological heterogeneity that influences testosterone-depression interactions. A genetically informed precision medicine approach using genes regulating testosterone levels and AR sensitivity is required.[115] The relationship between depressive symptoms and erectile dysfunction in middle-aged men is robust and independent of aging and para-aging confounders.[119] The association between depression, testosterone levels, and sexual symptoms in males is difficult to assess due to numerous confounding factors, such as medical conditions, obesity, smoking, alcohol use, diet, and stress. Testosterone and its metabolites act on many cerebral areas and modulate neurotransmission and mood disorders. In patients with severe depression or bipolar, testosterone therapy should be prescribed with caution because it can increase the risk of suicide attempters.[120] In conclusion, in hypogonadal men with dysthymic disorders, the therapy with testosterone can improve mood and mild depression, but in cases of severe depression, it should be used with caution. However, testosterone therapy has been associated with adverse cardiovascular events, such as increased risk of thrombosis, as well as psychiatric effects like mood swings and potential exacerbation of manic episodes in bipolar patients. These risks should be carefully weighed against its benefits in neurodegenerative and muscular conditions.

Conclusion

Testosterone significantly affects the brain and peripheral nervous system, maintaining neuronal health and functions. The action on the neurons is characterized by the presence of AR on the neuron body, dendrites, and axonal myelin. ARs are expressed in cortical area, hippocampus, hypothalamus, telencephalon, and amygdala, as well as in Purkinje cells of the cerebellar cortex. The neurodegenerative process is strongly sustained by oxidative stress in the brainstem and spinal cord areas associated with sensory functions. Testosterone and estradiol exert a strong anti-oxidative effect. Testosterone regulates neuronal growth, differentiation, and survival and stimulates oligodendrocytes, myelin repair, and axon regeneration. Myelin regeneration is the main objective of preventing and treating neurodegenerative diseases such as ALS and MS. Furthermore, testosterone inhibits the Aβ formation, exerting a protective effect on brain function and preserving Alzheimer's disease.

Neurogenesis occurs throughout adulthood in select brain regions. Unfortunately, only a few clinical studies investigating the effect of androgen on neurodegenerative disease have been conducted, so it becomes hard to draw significant conclusions. In aging, loss of muscular strength and physical disability are associated with denervation and muscle fiber atrophy, and the therapy with androgen is essential to stimulate the recovery process of reinnervation in the musculature of these debilitated patients. The use of testosterone replacement therapy is suggested in men with mood disorders with low plasma androgen levels. Still, the sole purpose of improving major depressive symptoms is not recommended, according to current evidence. Moreover, in patients with bipolar disorder, testosterone therapy should be carefully evaluated because testosterone treatment may increase the risk of manic episodes and suicide attempts. In conclusion, testosterone and its derivatives exert many beneficial effects on brain and neuronal function, and they should be considered more in clinical practice.

Acknowledgements

None.

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

1. Morley JE, Kaiser FE, Perry HM 3rd, et al. Longitudinal changes in testosterone, luteinizing hormone, and follicle-stimulating hormone in healthy older men. *Metabolism*. 1997;46(4):410–413.
2. Metter EJ, Conwit R, Tobin J, et al. Age-associated loss of power and strength in the upper extremities in women and men. *J Gerontol A Biol Sci Med Sci*. 1997;52(5):B267–B276.
3. Handelsman DJ. Testosterone and male aging: faltering hope for rejuvenation. *JAMA*. 2017;317(7):699–701.
4. Attard CC, Fava S. Benefits and risks of testosterone therapy in older men. *Minerva Urol Nefrol*. 2019;71(3):217–229.
5. Ishikawa T, Kenney CG, Jameson JL. Aromatase-independent testosterone conversion into estrogenic steroids is inhibited by a 5 alpha-reductase inhibitor. *J Steroid Biochem Mol Biol*. 2006;98(2):133–138.
6. Hussain R, Ghoumari AM, Bielecki B, et al. The neural androgen receptor: a therapeutic target for myelin repair in chronic demyelination. *Brain*. 2013;136(1):132–146.
7. Wang C, Jie C, Dai X. Possible roles of astrocytes in estrogen neuroprotection during cerebral ischemia. *Rev Neurosci*. 2014;25(3):255–268.
8. Kapoor D, Aldred H, Clark S, et al. Clinical and biochemical assessment of hypogonadism in men with type 2 diabetes: correlations with bioavailable testosterone and visceral adiposity. *Diabetes Care*. 2007;30(4):911–917
9. Bianchi VE, Locatelli V. Testosterone: a key factor in gender-related metabolic syndrome. *Obes Rev*. 2018;19(4):557–575.
10. Banks WA. Brain meets body: the blood-brain barrier as an endocrine interface. *Endocrinology*. 2012;153(9):4111–4119.
11. Sar M, Stumpf WE. Androgen concentration in motor neurons of cranial nerves and spinal cord. *Science*. 1977;197(4297):77–79.
12. Simerly RB, Chang C, Muramatsu M, et al. Distribution of androgen and estrogen receptor mRNA-containing cells in the rat brain: an in situ hybridization study. *J Comp Neurol*. 1990;294(1):76–95.
13. Mangelsdorf DJ, Thummel C, Beato M, et al. The nuclear receptor superfamily: the second decade. *Cell*. 1995;83(6):835–839.

14. Thomas PS Jr, Fraley GS, Damian V, et al. Loss of endogenous androgen receptor protein accelerates motor neuron degeneration and accentuates androgen insensitivity in a mouse model of X-linked spinal and bulbar muscular atrophy. *Hum Mol Genet*. 2006;15(14):2225–2238.

15. Matsumoto A. Hormonally induced neuronal plasticity in the adult motoneurons. *Brain Res Bull*. 1997;44(5):539–547.

16. DonCarlos LL, Ovejero DG, Sarkey S, et al. Androgen receptor immunoreactivity in forebrain axons and dendrites in the rat. *Endocrinology*. 2003;144(8):3632–3638.

17. Isgor C, Sengelaub DR. Prenatal gonadal steroids affect adult spatial behavior, CA1 and CA3 pyramidal cell morphology in rats. *Horm Behav*. 1998;34(2):183–198.

18. Pallares ME, Adrover E, Imsen M, et al. Maternal administration of flutamide during late gestation affects the brain and reproductive organs development in the rat male offspring. *Neuroscience*. 2014;278:122–135.

19. Rosario ER, Chang L, Stanczyk FZ, et al. Age-related testosterone depletion and the development of Alzheimer disease. *JAMA*. 2004;292(12):1431–1432.

20. Yan XS, Yang ZJ, Jia JX, et al. Protective mechanism of testosterone on cognitive impairment in a rat model of Alzheimer's disease. *Neural Regen Res*. 2019;14(4):649–657.

21. Huo DS, Sun JF, Zhang B, et al. Protective effects of testosterone on cognitive dysfunction in Alzheimer's disease model rats induced by oligomeric beta amyloid peptide 1-42. *J Toxicol Environ Health A*. 2016;79(16):856–863.

22. Gouras GK, Xu H, Gross RS, et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. *Proc Natl Acad Sci U S A*. 2000;97(3):1202–1205.

23. Pike CJ. Testosterone attenuates beta-amyloid toxicity in cultured hippocampal neurons. *Brain Res*. 2001;919(2):160–165.

24. Goodenough S, Engert S, Behl C. Testosterone stimulates rapid secretory amyloid precursor protein release from rat hypothalamic cells via the activation of the mitogen-activated protein kinase pathway. *Neurosci Lett*. 2000;296(1):49–52.

25. Meydan S, Kus I, Tas U, et al. Effects of testosterone on orchiectomy-induced oxidative damage in the rat hippocampus. *J Chem Neuroanat*. 2010;40(3):281–285.

26. Son SW, Lee JS, Kim HG, et al. Testosterone depletion increases the susceptibility of brain tissue to oxidative damage in a restraint stress mouse model. *J Neurochem*. 2016;136(1):106–117.

27. Urrego NT, Segura LMG, Echeverria V, et al. Testosterone protects mitochondrial function and regulates neuroglobin expression in astrocytic cells exposed to glucose deprivation. *Front Aging Neurosci*. 2016;8:152.

28. Ota H, Akishita M, Akiyoshi T, et al. Testosterone deficiency accelerates neuronal and vascular aging of SAMP8 mice: protective role of eNOS and SIRT1. *PLoS One*. 2012;7(12):e29598.

29. Ziehn MO, Avedisian AA, Dervin SM, et al. Therapeutic testosterone administration preserves excitatory synaptic transmission in the hippocampus during autoimmune demyelinating disease. *J Neurosci*. 2012;32(35):12312–12324.

30. Spritzer MD, Roy EA. Testosterone and adult neurogenesis. *Biomolecules*. 2020;10(2):225.

31. Hamson DK, Wainwright SR, Taylor JR, et al. Androgens increase survival of adult-born neurons in the dentate gyrus by an androgen receptor-dependent mechanism in male rats. *Endocrinology*. 2013;154(9):3294–3304.

32. Hammond J, Le Q, Goodyer C, et al. Testosterone-mediated neuroprotection through the androgen receptor in human primary neurons. *J Neurochem*. 2001;77(5):1319–1326.

33. Bianchi VE, Rizzi L, Bresciani E, et al. Androgen therapy in neurodegenerative diseases. *J Endocr Soc*. 2020;4(11):bvaa120.

34. Franklin RJ, Constant CF. Remyelination in the CNS: from biology to therapy. *Nat Rev Neurosci*. 2008;9(11):839–855.

35. Grimm A, Biliouris EE, Lang UE, et al. Sex hormone-related neurosteroids differentially rescue bioenergetic deficits induced by amyloid-beta or hyperphosphorylated tau protein. *Cell Mol Life Sci*. 2016;73(1):201–215.

36. McAllister C, Long J, Bowers A, et al. Genetic targeting aromatase in male amyloid precursor protein transgenic mice down-regulates beta-secretase (BACE1) and prevents Alzheimer-like pathology and cognitive impairment. *J Neurosci*. 2010;30(22):7326–7334.

37. Jaffe AB, Allerand CDT, Greengard P, et al. Estrogen regulates metabolism of Alzheimer amyloid beta precursor protein. J Biol Chem. 1994;269(17):13065–13068.

38. Scharfman HE, MacLusky NJ. Estrogen and brain-derived neurotrophic factor (BDNF) in hippocampus: complexity of steroid hormone-growth factor interactions in the adult CNS. *Front Neuroendocrinol*. 2006;27(4):415–435.

39. Li R, He P, Cui J, et al. Brain endogenous estrogen levels determine responses to estrogen replacement therapy via regulation of BACE1 and NEP in female Alzheimer's transgenic mice. *Mol Neurobiol*. 2013;47(3):857–867.

40. Manthey D, Heck S, Engert S, et al. Estrogen induces a rapid secretion of amyloid beta precursor protein via the mitogen-activated protein kinase pathway. *Eur J Biochem*. 2001;268(15):4285–4291.

41. Zhang Y, Champagne N, Beitel LK, et al. Estrogen and androgen protection of human neurons against intracellular amyloid beta1-42 toxicity through heat shock protein 70. *J Neurosci*. 2004;24(22):5315–5321.

42. Wang L, Pei JH, Jia JX, et al. Inhibition of oxidative stress by testosterone improves synaptic plasticity in senescence accelerated mice. *J Toxicol Environ Health A*. 2019;82(18):1061–1068.

43. Brand MD, Affourtit C, Esteves TC, et al. Mitochondrial superoxide: production, biological effects, and activation of uncoupling proteins. *Free Radic Biol Med*. 2004;37(6):755–767.

44. Foster TC, Kyritsopoulos C, Kumar A. Central role for NMDA receptors in redox mediated impairment of synaptic function during aging and Alzheimer's disease. *Behav Brain Res*. 2017;322:223–232.

45. Mota SI, Ferreira IL, Rego AC. Dysfunctional synapse in Alzheimer's disease - A focus on NMDA receptors. *Neuropharmacology*. 2014;76(Pt A):16–26.

46. Zhang Y, Li P, Feng J, et al. Dysfunction of NMDA receptors in Alzheimer's disease. *Neurol Sci*. 2016;37(7):1039–1047.

47. Verdile G, Laws SM, Henley D, et al. Associations between gonadotropins, testosterone, and beta amyloid in men at risk of Alzheimer's disease. *Mol Psychiatry*. 2014;19(1):69–75.

48. Gillett MJ, Martins RN, Clarnette RM, et al. Relationship between testosterone, sex hormone binding globulin and plasma amyloid beta peptide 40 in older men with subjective memory loss or dementia. *J Alzheimers Dis*. 2003;5(4):267–269.

49. Gandy S, Almeida OP, Fonte J, et al. Chemical andropause and amyloid-beta peptide. *JAMA*. 2001;285(17):2195–2196.

50. Almeida OP, Waterreus A, Spry N, et al. One year follow-up study of the association between chemical castration, sex hormones, beta-amyloid, memory and depression in men. *Psychoneuroendocrinology*. 2004;29(8):1071–1081.

51. Rosario ER, Chang L, Head EH, et al. Brain levels of sex steroid hormones in men and women during normal aging and in Alzheimer's disease. *Neurobiol Aging*. 2011;32(4):604–613.

52. Yang L, Zhou R. Effects of androgens on the amyloid beta protein in Alzheimer's disease. *Endocrinology*. 2018;159(12):3885–3894.

53. Rosario ER, Pike CJ. Androgen regulation of beta-amyloid protein and the risk of Alzheimer's disease. *Brain Res Rev*. 2008;57(2):444–453.

54. Lee JH, Byun MS, Yi D, et al. Sex-specific association of sex hormones and gonadotropins, with brain amyloid and hippocampal neurodegeneration. Neurobiol Aging. 2017;58:34–40.

55. Raghava N, Das BC, Ray SK. Neuroprotective effects of estrogen in CNS injuries: insights from animal models. *Neurosci Neuroecon*. 2017;6:15–29.

56. Sun M, Cole AP, Hanna N, et al. Cognitive impairment in men with prostate cancer treated with androgen deprivation therapy: a systematic review and meta-analysis. *J Urol*. 2018;199(5):1417–1425.

57. Siebert AL, Carr LL, Morgans AK. Neuropsychiatric impact of androgen deprivation therapy in patients with prostate cancer: current evidence and recommendations for the clinician. *Eur Urol Focus*. 2020;6(6):1170–1179.

58. Nead KT, Sinha S, Nguyen PL. Androgen deprivation therapy for prostate cancer and dementia risk: a systematic review and meta-analysis. *Prostate Cancer Prostatic Dis*. 2017;20(3):259–264.

59. Resnick SM, Matsumoto AM, Shields AJS, et al. Testosterone treatment and cognitive function in older men with low testosterone and age-associated memory impairment. *JAMA*. 2017;317(7):717–727.

60. Wahjoepramono EJ, Asih PR, Aniwiyanti V, et al. The effects of testosterone supplementation on cognitive functioning in older men. *CNS Neurol Disord Drug Targets*. 2016;15(4):337–343.

61. Asih PR, Wahjoepramono EJ, Aniwiyanti V, et al. Testosterone replacement therapy in older male subjective memory complainers: double-blind randomized crossover placebo-controlled clinical trial of physiological assessment and safety. *CNS Neurol Disord Drug Targets*. 2015;14(5):576–586.

62. Cherrier MM, Anderson K, Shofer J, et al. Testosterone treatment of men with mild cognitive impairment and low testosterone levels. *Am J Alzheimers Dis Other Demen*. 2015;30(5):421–430.

63. Borst SE, Yarrow JF, Fernandez C, et al. Cognitive effects of testosterone and finasteride administration in older hypogonadal men. *Clin Interv Aging*. 2014;9:1327–1333.

64. Young LA, Neiss MB, Samuels MH, et al. Cognition is not modified by large but temporary changes in sex hormones in men. *J Clin Endocrinol Metab*. 2010;95(1):280–288.

65. Vonk MHE, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA*. 2008;299(1):39–52.

66. Vaughan C, Goldstein FC, Tenover JL. Exogenous testosterone alone or with finasteride does not improve measurements of cognition in healthy older men with low serum testosterone. *J Androl*. 2007;28(6):875–882.

67. Maki PM, Ernst M, London ED, et al. Intramuscular testosterone treatment in elderly men: evidence of memory decline and altered brain function. *J Clin Endocrinol Metab*. 2007;92(11):4107–4114.

68. Cherrier MM, Matsumoto AM, Amory JK, et al. Characterization of verbal and spatial memory changes from moderate to supraphysiological increases in serum testosterone in healthy older men. *Psychoneuroendocrinology*. 2007;32(1):72–79.

69. Lu PH, Masterman DA, Mulnard R, et al. Effects of testosterone on cognition and mood in male patients with mild Alzheimer disease and healthy elderly men. *Arch Neurol*. 2006;63(2):177–185.

70. Haren MT, Wittert GA, Chapman IM, et al. Effect of oral testosterone undecanoate on visuospatial cognition, mood, and quality of life in elderly men with low-normal gonadal status. *Maturitas*. 2005;50(2):124–133.

71. Kenny AM, Fabregas G, Song C, et al. Effects of testosterone on behavior, depression, and cognitive function in older men with mild cognitive loss. *J Gerontol A Biol Sci Med Sci*. 2004;59(1):75–78.

72. Tan RS, Pu SJ. A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male*. 2003;6(1):13–17.

73. O'Connor DB, Archer J, Hair WM, et al. Activational effects of testosterone on cognitive function in men. *Neuropsychologia*. 2001;39(13):1385–1394.

74. Cherrier MM, Asthana S, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology*. 2001;57(1):80–88.

75. Mohamad NV, Nirwana SI, Chin KY. A Review on the Effects of Testosterone Supplementation in Hypogonadal Men with Cognitive Impairment. *Curr Drug Targets*. 2018;19(8):898–906.

76. Beauchet O. Testosterone and cognitive function: current clinical evidence of a relationship. *Eur J Endocrinol*. 2006;155(6):773–781.

77. Roeck EED, Deyn PPD, Dierckx E, et al. Brief cognitive screening instruments for early detection of Alzheimer's disease: a systematic review. *Alzheimers Res Ther*. 2019;11(1):21.

78. Kalincik T, Vivek V, Jokubaitis V, et al. Sex as a determinant of relapse incidence and progressive course of multiple sclerosis. *Brain*. 2013;136(11):3609–3617.

79. Gold SM, Voskuhl RR. Estrogen and testosterone therapies in multiple sclerosis. *Prog Brain Res*. 2009;175:239–251.

80. Kurth F, Luders E, Sicotte NL, et al. Neuroprotective effects of testosterone treatment in men with multiple sclerosis. *Neuroimage Clin*. 2014;4:454–460.

81. Martin LJ, Price AC, Kaiser A, et al. Mechanisms for neuronal degeneration in amyotrophic lateral sclerosis and in models of motor neuron death (Review). *Int J Mol Med*. 2000;5(1):3–13.

82. Esperante IJ, Meyer M, Banzan C, et al. Testosterone reduces myelin abnormalities in the wobbler mouse model of amyotrophic lateral sclerosis. *Biomolecules*. 2024;14(4):428.

83. Lara A, Esperante I, Meyer M, et al. Neuroprotective effects of testosterone in male wobbler mouse, a model of amyotrophic lateral sclerosis. *Mol Neurobiol*. 2021;58(5):2088–2106.

84. Kaspar BK, Frost LM, Christian L, et al. Synergy of insulin-like growth factor-1 and exercise in amyotrophic lateral sclerosis. *Ann Neurol*. 2005;57(5):649–655.

85. Wang Y, Kreisberg JI, Ghosh PM. Cross-talk between the androgen receptor and the phosphatidylinositol 3-kinase/Akt pathway in prostate cancer. *Curr Cancer Drug Targets*. 2007;7(5):591–604.

86. Bjornebekk A, Scarth M, Neupane SP, et al. Use of high-dose androgens is associated with reduced brain-derived neurotrophic factor in male weightlifters. *Neuroendocrinology*. 2023;113(1):36–47.

87. Yoo YE, Ko CP. Dihydrotestosterone ameliorates degeneration in muscle, axons and motoneurons and improves motor function in amyotrophic lateral sclerosis model mice. *PLoS One*. 2012;7(9):e37258.

88. Mentis AA, Bougea AM, Chrousos GP. Amyotrophic lateral sclerosis (ALS) and the endocrine system: Are there any further ties to be explored? *Aging Brain*. 2021;1(1):100024.

89. Griggs RC, Kingston W, Jozefowicz RF, et al. Effect of testosterone on muscle mass and muscle protein synthesis. *J Appl Physiol (1985)*. 1989;66(2):498–503.

90. Herbst KL, Bhasin S. Testosterone action on skeletal muscle. *Curr Opin Clin Nutr Metab Care*. 2004;7(3):271–277.

91. Kruse R, Petersson SJ, Christensen LL, et al. Effect of long-term testosterone therapy on molecular regulators of skeletal muscle mass and fibre-type distribution in aging men with subnormal testosterone. *Metabolism*. 2020;112:154347.

92. Ferrando AA, Moore MS, Yeckel CW, et al. Testosterone administration to older men improves muscle function: molecular and physiological mechanisms. *Am J Physiol Endocrinol Metab*. 2002;282(3):E601–E607.

93. Bhasin S, Woodhouse L, Storer TW. Proof of the effect of testosterone on skeletal muscle. *J Endocrinol*. 2001;170(1):27–38.

94. Coletti C, Acosta GF, Keslacy S, et al. Exercise-mediated reinnervation of skeletal muscle in elderly people: An update. *Eur J Transl Myol*. 2022;32(1):10416.

95. Larsson L, Degens H, Li M, et al. Sarcopenia: Aging-Related Loss of Muscle Mass and Function. *Physiol Rev*. 2019;99(1):427–511.

96. Mosole S, Carraro U, Kern H, et al. Long-term high-level exercise promotes muscle reinnervation with age. *J Neuropathol Exp Neurol*. 2014;73(3):284–294.

97. Bianchi V, Marbini A. Neuroregenerative effect of oxandrolone: A case report. *Am J Case Rep*. 2015;16:763–767.

98. Connor SG, Fairchild TJ, Learmonth YC, et al. Testosterone treatment combined with exercise to improve muscle strength, physical function and quality of life in men affected by inclusion body myositis: A randomised, double-blind, placebo-controlled, crossover trial. *PLoS One*. 2023;18(1):e0283394.

99. Green DJ, Chasland LC, Yeap BB, et al. Comparing the impacts of testosterone and exercise on lean body mass, strength and aerobic fitness in aging men. *Sports Med Open*. 2024;10(1):30.

100. Bhasin S, Seidman S. Testosterone Treatment of Depressive Disorders in Men: Too Much Smoke, Not Enough High-Quality Evidence. *JAMA Psychiatry*. 2019;76(1):9–10.

101. Shores MM, Sloan KL, Matsumoto AM, et al. Increased incidence of diagnosed depressive illness in hypogonadal older men. *Arch Gen Psychiatry*. 2004;61(2):162–167.

102. Connor EB, Muhlen DGV, Silverstein DK. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab*. 1999;84(2):573–577.

103. Fischer S, Ehlert U, Castro RA. Hormones of the hypothalamic-pituitary-gonadal (HPG) axis in male depressive disorders: A systematic review and meta-analysis. *Front Neuroendocrinol*. 2019;55:100792.

104. Giltay EJ, Mast RCVD, Lauwen E, et al. Plasma testosterone and the course of major depressive disorder in older men and women. *Am J Geriatr Psychiatry*. 2017;25(5):425–437.

105. Giltay EJ, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on depressive symptoms and sexual dysfunction in hypogonadal men with the metabolic syndrome. *J Sex Med*. 2010;7(7):2572–2582.

106. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab*. 2002;87(2):589–598.

107. Mazur A. Biosocial models of deviant behavior among male army veterans. *Biol Psychol*. 1995;41(3):271–293.

108. Ford AH, Yeap BB, Flicker L, et al. Prospective longitudinal study of testosterone and incident depression in older men: The Health In Men Study. *Psychoneuroendocrinology*. 2016;64:57–65.

109. Seidman SN, Araujo AB, Roose SP, et al. Low testosterone levels in elderly men with dysthymic disorder. *Am J Psychiatry*. 2002;159(3):456–459.

110. Barriere DA, Ella A, Adriaensen H, et al. In vivo magnetic resonance imaging reveals the effect of gonadal hormones on morphological and functional brain sexual dimorphisms in adult sheep. *Psychoneuroendocrinology*. 2019;109:104387.

111. Zitzmann M, Weckesser M, Schober O, et al. Changes in cerebral glucose metabolism and visuospatial capability in hypogonadal males under testosterone substitution therapy. *Exp Clin Endocrinol Diabetes*. 2001;109(6):302–304.

112. Indirli R, Lanzi V, Arosio M, et al. The association of hypogonadism with depression and its treatments. *Front Endocrinol (Lausanne)*. 2023;14:1198437.

113. Handelsman DJ, Wittert GA. Testosterone and depression symptoms in aging men. *J Clin Endocrinol Metab*. 2024;109(6):e1798–e1799.

114. Morssinkhof MWL, Wylick DWV, Vink SP, et al. Associations between sex hormones, sleep problems and depression: a systematic review. *Neurosci Biobehav Rev*. 2020;118:669–680.

115. Hauger RL, Saelzler UG, Pagadala MS, et al. The role of testosterone, the androgen receptor, and hypothalamic-pituitary-gonadal axis in depression in ageing men. *Rev Endocr Metab Disord*. 2022;23(4):1259–1273.

116. Grossmann M, Robledo KP, Daniel M, et al. Testosterone treatment, weight loss, and health-related quality of life and psychosocial function in men: A 2-year randomized controlled trial. *J Clin Endocrinol Metab*. 2024;109(6):2019–2028.

117. Zitzmann M. Testosterone, mood, behaviour and quality of life. *Andrology*. 2020;8(6):1598–1605.

118. Zarrouf FA, Artz S, Griffith J, et al. Testosterone and depression: systematic review and meta-analysis. *J Psychiatr Pract*. 2009;15(4):289–305.

119. Takao T, Tsujimura A, Okuda H, et al. Lower urinary tract symptoms and erectile dysfunction associated with depression among Japanese patients with late-onset hypogonadism symptoms. *Aging Male*. 2011;14(2):110–114.

120. Sher L, Grunebaum MF, Sullivan GM, et al. Testosterone levels in suicide attempters with bipolar disorder. *J Psychiatr Res*. 2012;46(9):1267–1271.