Title

Increased sexual desire with exogenous testosterone administration in men with obstructive sleep apnea: a randomized placebo-controlled study

Journal

Andrology, 4(1)

ISSN

2047-2919

Authors

Melehan, KL
Hoyos, CM
Yee, BJ
et al.

Publication Date

2016

DOI

10.1111/andr.12132

Peer reviewed

HHS Public Access

Author manuscript

Andrology. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

Andrology. 2016 January ; 4(1): 55–61. doi:10.1111/andr.12132.

Increased sexual desire with exogenous testosterone administration in men with obstructive sleep apnea: a randomized placebo-controlled study

K. L. Melehan[1,2,3,a], **C. M. Hoyos**[1,2,a], **B. J. Yee**[1,2,3], **K. K. Wong**[1,2,3], **P. R. Buchanan**[1,4], **R. R. Grunstein**[1,2,3], and **P. Y. Liu**[1,2,5]

[1]NHMRC Centre for The Integrated Research and Understanding of Sleep, Woolcock Institute of Medical Research, NSW, Australia

[2]Sydney Medical School, University of Sydney, Sydney, NSW, Australia

[3]Department of Respiratory and Sleep Medicine, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

[4]Department of Respiratory Medicine, Liverpool Hospital, Sydney, NSW, Australia

[5]Division of Endocrinology, Department of Medicine, David Geffen School of Medicine at UCLA, Harbor-UCLA Medical Center and Los Angeles Biomedical Research Institute, Los Angeles, CA, USA

SUMMARY

Testosterone (T) deficiency, sexual dysfunction, obesity and obstructive sleep apnea (OSA) are common and often coexist. T prescriptions have increased worldwide during the last decade, including to those with undiagnosed or untreated OSA. The effect of T administration on sexual function, neurocognitive performance and quality of life in these men is poorly defined. The aim of this study was to examine the impact of T administration on sexual function, quality of life and neurocognitive performance in obese men with OSA. We also secondarily examined whether baseline T might modify the effects of T treatment by dichotomizing on baseline T levels pre-specified at 8, 11 and 13 nmol/L. This was a randomized placebo-controlled study in which 67 obese men with OSA (mean age 49 ± 1.3 years) were randomized to receive intramuscular injections of either 1000 mg T undecanoate or placebo at baseline, week 6 and week 12. All participants were concurrently enrolled in a weight loss program. General and sleep-related quality of life, neurocognitive performance and subjective sexual function were assessed before and 6, 12 and 18 weeks after therapy. T compared to placebo increased sexual desire ($p = 0.004$) in all men, irrespective of baseline T levels. There were no differences in erectile function, frequency of

Correspondence: Peter Y. Liu, 1124 W. Carson Street, Torrance, CA 90502, USA. pliu@labiomed.org.

[a]Co-first authors.

DISCLOSURES

The authors have no conflicts to disclose.

AUTHORS' CONTRIBUTIONS

KM and CH contributed equally to the publication including data collection, statistical analysis, data interpretation and manuscript preparation. BY, KW and PB contributed to data collection, data interpretation and manuscript review. RG contributed to protocol development and manuscript review. PL conceived and designed the study, obtained funding, interpreted data, prepared and reviewed the manuscript and supervised all aspects of the study.

sexual attempts, orgasmic ability, general or sleep-related quality of life or neurocognitive function (all p = NS). In those with baseline T levels below 8 nmol/L, T increased vitality (p = 0.004), and reduced reports of feeling down (p = 0.002) and nervousness (p = 0.03). Our findings show that 18 weeks of T therapy increased sexual desire in obese men with OSA independently of baseline T levels whereas improvements in quality of life were evident only in those with T levels below 8 nmol/L. These small improvements would need to be balanced against potentially more serious adverse effects of T therapy on breathing.

Keywords

neurocognitive function; obstructive sleep apnea; sexual desire; testosterone supplementation

INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition which affects approximately one in four middle-aged men. OSA is characterized by repetitive frequent complete and partial upper airway closures that cause blood oxygen desaturation and arousals (awakenings) from sleep. Biochemical androgen deficiency is independently associated with OSA and up to 40% of men with OSA have serum testosterone (T) levels in the young adult hypogonadal range (Luboshitzky *et al.*, 2002; Gambineri *et al.*, 2003; Ak *et al.*, 2013). Furthermore, T concentrations are lower in those with more severe OSA, particularly more severe hypoxemia, and OSA treatment with continuous positive airway pressure increases T (Grunstein *et al.*, 1989; Luboshitzky *et al.*, 2003). Putative central mechanisms by which OSA decreases T include interruption of pulsatile luteinizing hormone secretion by sleep restriction (Leproult & Van Cauter, 2011), sleep fragmentation (Luboshitzky *et al.*, 2003) and/or repetitive hypoxia (Gambineri *et al.*, 2003). Obesity, in particular central obesity, is recognized as the most specific sign associated with androgen deficiency (Buvat *et al.*, 2013; Corona *et al.*, 2013) and is also independently associated with OSA, and the combination of both OSA and obesity may further potentiate declines in circulating T (Liu *et al.*, 2007).

Reduced sexual desire and erectile quality, low mood and cognitive impairment are symptoms common to both OSA (Budweiser *et al.*, 2009; Jackson *et al.*, 2011) and androgen deficiency (Rajfer, 2000; Janowsky, 2006; Travison *et al.*, 2006). In a healthy population without comorbid disease, a single clinically meaningful cut-off to classify symptomatic androgen deficiency is not possible, as different symptoms become apparent at various thresholds of T ranging from 8 to 12 nmol/L (Kelleher *et al.*, 2004; Wang *et al.*, 2009). For example, fewer morning erections occur in men with T concentrations below 11–13 nmol/L (Seftel *et al.*, 2004; Wu *et al.*, 2010), erectile function is impaired below 8 nmol/L (Wu *et al.*, 2010) and sexual desire is reduced below 5–15 nmol/L (Salmimies *et al.*, 1982; Seftel *et al.*, 2004; Zitzmann *et al.*, 2006; Wu *et al.*, 2010). Other thresholds have also been defined for quality of life related to vigor, walking more than 1 km, bending and stooping, feeling downhearted, loss of energy and fatigue (Wu *et al.*, 2010). Hence there appears to be different thresholds for the appearance of symptomatic androgen deficiency in the healthy male population, but how or whether these thresholds apply to men with specific comorbid diseases is poorly defined, even for common comorbid conditions. The European Male

Aging study demonstrated that sexual function is the most specific symptom associated with T deficiency (Wu *et al.*, 2010) whereas other psychological and physical symptoms are less specific and could be confused with symptoms of aging. Ultimately, establishing that T treatment actually improves symptoms will be required. In this respect, several small studies have reported improvements in memory and spatial cognition after T administration in older men, but generally only in those who had a lower baseline level of T (Cherrier *et al.*, 2003; Janowsky, 2006).

No study to date has systematically examined the effect of T therapy on sexual function, neurocognitive function and reduced quality of life in men with OSA. This is relevant because obese men with OSA are at increased risk for sexual dysfunction, neurocognitive impairment and reduced quality of life (Young *et al.*, 2002; Budweiser *et al.*, 2009; Quan *et al.*, 2011). The focus of this report was to examine the impact of standard dose T supplementation on sexual function, general and disease-specific quality of life and cognitive function in a randomized placebo controlled study of obese men with OSA. We also explored whether baseline T levels influenced these treatment effects. The primary purpose of the overall study, however, was to determine the effects of T treatment on sleep disordered breathing and cardio- metabolic health, both of which have been reported (Hoyos *et al.*, 2012a,b).

MATERIALS AND METHODS

Participants

Participants were recruited from sleep disorders clinics at Royal Prince Alfred Hospital and the Woolcock Institute of Medical Research, Sydney, Australia. Participants were deemed eligible to take part if they were men aged over 18, obese (body mass index >30 kg/m^2) and had at least mild OSA (apnea hypopnea index >10 events per hour). The exclusion criteria are described in detail elsewhere (Hoyos *et al.*, 2012a,b). A standard medical history, physical examination and blood samples were obtained upon entry to the study. All subjects provided written informed consent and the study was approved by the Sydney South West Area Health Service Human Research and Ethics Committee (Royal Prince Alfred Hospital Zone). All procedures complied with Good Clinical Practice guidelines, applicable regulatory requirements and the Declaration of Helsinki. The study is registered with the Australia New Zealand Clinical Trials Network (number ACTRN12606000404527).

Study design

This study was a randomized double-blind, placebo-controlled parallel group study. All participants were randomly assigned to receive three intramuscular injections of either T undecanoate 1000 mg (Reandron; Bayer Schering, Berlin, Germany) or matching placebo, also supplied by the manufacturer. A registered nurse administered these injections at baseline, week 6 and week 12. In addition, all participants undertook a concurrent weight loss program, consisting of a dietician-prescribed 2500 kJ (600 kcal) daily deficit diet and exercise advice (at least 30 min brisk walking per day) previously described in detail (Hoyos *et al.*, 2012a,b). Sexual function, quality of life and neurocognition were assessed at baseline, and at weeks 6, 12 and 18.

Hormone analysis

Venous blood samples were collected in the early morning at baseline and at weeks 6, 7, 12 and 18. Luteinizing hormone, follicle- stimulating hormone and total T were measured, and free T calculated using the Vermeulen formula (Vermeulen *et al.*, 1999). Blood samples were stored at −80 °C and batched for assaying. All samples from each individual participant were performed in the same assay.

Sexual function and quality of life

A series of questionnaires regarding quality of life, levels of sleepiness and sexual function were administered in an isolated room to maintain privacy at baseline, weeks 6, 12 and 18. General and sleep-related quality of life was assessed using the Short Form 36 (SF-36) (Ware & Sherbourne, 1992) and functional outcome of sleep (FOSQ) (Weaver *et al.*, 1997) questionnaires, respectively. Analyses were performed on aggregated data using established scoring algorithms for various domains, as well as on single individual items of specific questionnaires that had previously been found to be associated with T levels (Weaver *et al.*, 1997; Wu *et al.*, 2010). These questions related to feeling down and being a nervous person as well as the impact of health upon the ability to do vigorous activity, walking 1 km, and bending and kneeling. Self-rated levels of sleepiness over the last 2 weeks were assessed by the Epworth Sleepiness Scale and momentary sleepiness by the Karolinska and Stanford Sleepiness Scales (Johns, 2008).

Various facets of sexual function were measured by the visual analogue scale (Fennell *et al.*, 2010). Participants were asked eight questions regarding their degree of sexual thought, desire, erectile and ejaculatory function, as well as sexual frequency and satisfaction. Responses were expressed on a 0–1.0 scale.

Neurocognitive performance

Computerized neurocognitive function testing was conducted at the same time of day for each participant at baseline, 6, 12 and 18 weeks. Spatial cognition was assessed using the ‘Tower of London’ (Shallice, 1982), a task-based test in which balls must be moved into a pre-specified position in the least amount of moves. Executive memory was measured by the ‘Stroop’ test in which a series of words describing various colors were presented in different colored fonts. Participants were required to identify the color of the word, rather than the meaning of the word itself (Stroop, 1935). Reaction time was assessed using the psychomotor vigilance task (PVT) in which the subject pressed a button in response to a stimuli which recorded as well as displayed to the subject each reaction time in milliseconds (Dinges & Powell, 1985).

Statistical analysis

Statistical analyses were performed using SAS statistical package version 9.2 (SAS Institute, Cary, NC, USA). Significant differences were defined at $p < 0.05$. The randomization code was broken only after all data were collected and the database was cleaned and locked.

Outcome variables were differences from baseline at 6, 12 and 18 weeks with all analyses performed by intention-to-treat. Mixed model analysis was used to determine the overall

change from baseline. Within-group changes as well as between-group differences were assessed using models of treatment, time and its interaction. The influence of baseline T (total and free) on the effectiveness of T treatment was also explored on all outcomes. Baseline total and free T were included in separate mixed models as dichotomized factors using predefined cut points of baseline total T (8, 11 and 13 nmol/L) and free T (160, 220 and 280 pmol/L). These thresholds had been previously identified for a range of symptoms from a large population-representative cohort (Wu *et al.*, 2010). These models consisted of baseline T, treatment and its interaction. The interaction terms were examined, and if statistically significant, post hoc analyses comparing treatment effects at each strata of baseline T were performed. Significant interactions are illustrated in graphs where groups are stratified by both baseline T and treatment.

Additionally, in order to examine for a continuous effect of baseline total and free T, these were separately included in individual models as linear covariates. A separate analysis to examine for the continuous effect of age was also conducted.

RESULTS

The flow of participants throughout the study has been reported previously (Hoyos *et al.*, 2012a,b). Briefly, 54 participants completed the study (26 and 28 in T and placebo groups, respectively). Two participants who withdrew early from the study attended an exit visit and completed several procedures including the questionnaires. These results were recorded as their final study results (i.e. week 18). The baseline characteristics of the 67 men who were randomized into the protocol are shown in Table 1. There were no significant differences between the groups at baseline.

As expected, men who received active treatment showed increases in serum T and significant decreases in follicular stimulating hormone and luteinizing hormone compared to those in the placebo group as described previously (Hoyos *et al.*, 2012a, b). T treatment increased sexual desire compared to placebo (Figs 1 & 2). This between-group difference first detected at week 6 ($p = 0.0073$) remained for the duration of the study and was independent of baseline T levels. There were no between-group differences in any other sexual function outcome including the number of sexual encounters, erectile or ejaculatory function (Fig. 2). Subjective sleepiness, SF36 and FOSQ domains and single questions did not differ between the two groups (p = NS, data not shown). T, compared to placebo, treatment did not change neurocognitive function as measured by the Stroop, Tower of London and PVT (Table 2). There was no difference in weight loss between the two groups ($p = 0.16$). After stratification, 62, 47 and 23% of participants had baseline T concentrations that were less than 13, 11 and 8 nmol/L, respectively. The interaction term of treatment and baseline total T dichotomized at a level of 8 nmol/L was statistically significant for degree of feeling down ($p = 0.004$), vitality ($p = 0.01$) and nervousness ($p = 0.04$), showing that the effect of the treatment was influenced by baseline T levels (Fig. 3). Post hoc analyses showed between-group differences between T and placebo-treated men with baseline total T of less than 8 nmol/L: improvements in feeling down ($p = 0.0021$), vitality ($p = 0.004$) and nervousness ($p = 0.04$). In contrast, there were no between-group differences between T and placebo-treated men with baseline total T levels above 8 nmol/L (all p = NS) (Fig. 3). For all

measured parameters mentioned, analogous analyses dichotomizing on predefined free T thresholds did not reveal any significant findings (data not shown). Furthermore, baseline total or free T concentrations had no influence on any other outcomes including any of the sexual parameters. Adding baseline total or free T concentrations or age as continuous covariates in separate mixed models did not alter the significance of any of the between-group associations (data not shown).

DISCUSSION

This is the first randomized controlled study to investigate the effects of exogenous T supplementation on sexual function, quality of life and neurocognitive performance in obese men with OSA undergoing a weight loss program, but not otherwise being treated for OSA. We show that T administration, compared to placebo, increases sexual desire across a range of baseline T levels, but had no effect on erectile function, neurocognitive function or overall quality of life. Vitality, downheartedness and nervousness improved, but only in those with baseline T < 8 nmol/L. Sexual desire increased 6 weeks after a single standard dose of T undeconate and remained increased until the end of the study.

The effect of T on sexual desire did not depend on baseline (untreated) blood T concentrations: a consistent finding confirmed by extensive analyses incorporating baseline T as a continuous linear variable, and as dichotomized factors using three pre-defined cut points. The current findings are in line with a recent meta-analysis of randomized controlled studies evaluating the effect of T on sexual parameters (Corona *et al.*, 2014). In particular, the meta-analysis found that T supplementation did not improve erectile function in a population of both hypogonadal and eugonadal participants, as seen in the current study. Conversely, a positive effect on sexual desire could be observed even for patients with higher baseline T levels (>12 nM). Other randomized controlled trials have shown improvements in several aspects of sexual function in other populations – for example, improvements in erectile function, intercourse satisfaction, sexual desire, overall satisfaction and orgasm in men with type 2 diabetes mellitus (Hackett *et al.*, 2013) as well as erectile function and sexual quality of life in men with chronic obstructive pulmonary disease (Svartberg *et al.*, 2004). In contrast, other randomized controlled trials of T therapy show small, variable and inconsistent improvements in erectile function, sexual desire or sexual function (Svartberg *et al.*, 2004; Bolona *et al.*, 2007; Gianatti *et al.*, 2014) and contradictory findings showing greatest effects in those with (Gianatti *et al.*, 2014; Isidori *et al.*, 2014) or without (Bolona *et al.*, 2007) lower baseline T blood concentrations. For these reasons, collecting more data in well-characterized cohorts known to have sexual problems, such as men with OSA or diabetes mellitus, or simply otherwise healthy older men, may better resolve these contradictions. Better characterization of specific subject characteristics to predict better or worse response to T therapy is required.

Although other sexual activity domains did not improve, this may be due to relationship or social factors or no improvement in erectile function. Participants were not included on the basis of relationship status, and may not have had a regular partner during the study which would have curtailed the number of sexual attempts; non-partnered masturbation frequency declines with age, and both partnered sexual intercourse and non-partnered masturbation

frequency are likely to be lower in those with OSA due to concurrent poor health (Reece *et al.*, 2010). An alternate explanation is that T therapy increases libido, but this simply does not translate into a detectable increase in sexual activity because the effect on libido was small and insufficient to motivate men to seek sexual activity. Additionally, 3 months of treatment may have been too short to see an improvement in erectile function, which may take a full year to achieve maximal response (Saad *et al.*, 2011).

The lack of improvement in sleepiness and sleep-related quality of life is supported by the only other study reporting these outcomes in men with OSA which used higher doses of T than the present study (Liu *et al.*, 2003). General quality of life, as assessed by the overall domains of the SF-36, was also unchanged which is consistent with a previous randomized controlled study in older men (Emmelot-Vonk *et al.*, 2008). Previous studies have shown that some individual questions on the SF-36 are related to the level of T (Wu *et al.*, 2010). The current study is consistent with presumptive thresholds in quality of life measures for not only symptoms, but in response to T therapy as we showed improvements in feeling down, vitality and nervousness in participants with baseline total T blood levels <8 nmol/L.

Testosterone therapy did not change neurocognitive measures of spatial ability, executive memory or reaction time. This is consistent with recent work that also found no change in executive function, memory and spatial cognition using large doses of T in presumably healthy young and older men without comorbid disorders (Young *et al.*, 2010), although earlier smaller studies have reported improvements in memory and spatial cognition (Cherrier *et al.*, 2003; Janowsky, 2006). Well-described cognitive changes have been described in men with OSA, including those with moderate to severe OSA similar to those in this report.

Although the effect of T on sexual function was not the primary outcome for this study, these outcomes are of interest, given the known effects in the non-OSA population. The randomized controlled design allows comparison between groups, despite participants not being included on the basis of symptoms or relationship status.

In conclusion, T therapy improved sexual desire in obese men with OSA regardless of baseline T levels in this 18 week study. There were no overall changes in neurocognition or quality of life; however, those with lower levels of baseline total T were shown to improve in the domains of vitality, feeling down and nervousness, as measured by the SF-36. Larger and longer term studies would be required to confirm persistence of improvements. These improvements in quality of life parameters, particularly in those with lower baseline T, need to be balanced against potential risks of T therapy, including potentially worsening OSA.

Acknowledgments

We thank the Data and Safety Monitoring Committee which consisted of Professor Michael Hensley (chair), Associate Professor Val Gebski and Professor Stephen Twigg. We also thank the men who participated in the study, the sleep physicians, research nurses, the study co-ordinators and Farid Saad. The study was supported by the National Health and Medical Research Council of Australia (NHMRC) through a project grant (512499), a Centre for Clinical Research Excellence in Interdisciplinary Sleep Health (571421) and fellowships to KM, CH, RRG and PYL (633166, 512057633166, 51202916 and 1025248, respectively). PYL was also supported by the National Center for Advancing Translational Sciences through UCLA CTSI Grant UL1TR000124 and R01 HL124211-01. Bayer Schering supplied study drug, matching placebo and $20 000 to date.

References

Ak M, Balikci A, Haciomeroglu B, Zincir S, Cinar A, Congologlu E, Bozkurt A, Ozgen F, Ozsahin A. Quality of sexual life in men with obstructive sleep apnoea. J Health Psychol. 2013; 18:245–251. [PubMed: 22419417]

Bolona ER, Uraga MV, Haddad RM, Tracz MJ, Sideras K, Kennedy CC, Caples SM, Erwin PJ, Montori VM. Testosterone use in men with sexual dysfunction: a systematic review and metaanalysis of randomized placebo-controlled trials. Mayo Clin Proc. 2007; 82:20–28. [PubMed: 17285782]

Budweiser S, Enderlein S, Jorres RA, Hitzl AP, Wieland WF, Pfeifer M, Arzt M. Sleep apnea is an independent correlate of erectile and sexual dysfunction. J Sex Med. 2009; 6:3147–3157. [PubMed: 19570042]

Buvat J, Maggi M, Guay A, Torres LO. Testosterone deficiency in men: systematic review and standard operating procedures for diagnosis and treatment. J Sex Med. 2013; 10:245–284. [PubMed: 22971200]

Cherrier MM, Craft S, Matsumoto AH. Cognitive changes associated with supplementation of testosterone or dihydrotestosterone in mildly hypogonadal men: a preliminary report. J Androl. 2003; 24:568–576. [PubMed: 12826696]

Corona G, Rastrelli G, Maggi M. Diagnosis and treatment of late-onset hypogonadism: systematic review and meta-analysis of TRT outcomes. Best Pract Res Clin Endocrinol Metab. 2013; 27:557–579. [PubMed: 24054931]

Corona G, Isidori AM, Buvat J, Aversa A, Rastrelli G, Hackett G, Rochira V, Sforza A, Lenzi A, Mannucci E, Maggi M. Testosterone supplementation and sexual function: a meta-analysis study. J Sex Med. 2014; 11:1577–1592. [PubMed: 24697970]

Dinges D, Powell J. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. Behav Res Meth Ins C. 1985; 17:652–655.

Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, Aleman A, Lock TM, Bosch JL, Grobbee DE, van der Schouw YT. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. JAMA. 2008; 299:39–52. [PubMed: 18167405]

Fennell C, Sartorius G, Ly LP, Turner L, Liu PY, Conway AJ, Handelsman DJ. Randomized cross-over clinical trial of injectable vs. implantable depot testosterone for maintenance of testosterone replacement therapy in androgen deficient men. Clin Endocrinol (Oxf). 2010; 73:102–109. [PubMed: 19891698]

Gambineri A, Pelusi C, Pasquali R. Testosterone levels in obese male patients with obstructive sleep apnea syndrome: relation to oxygen desaturation, body weight, fat distribution and the metabolic parameters. J Endocrinol Invest. 2003; 26:493–498. [PubMed: 12952360]

Gianatti EJ, Dupuis P, Hoermann R, Zajac JD, Grossmann M. Effect of testosterone treatment on constitutional and sexual symptoms in men with type 2 diabetes in a randomized, placebo-controlled clinical trial. J Clin Endocrinol Metab. 2014; 99:3821–3828. [PubMed: 24978674]

Grunstein RR, Handelsman DJ, Lawrence SJ, Blackwell C, Caterson ID, Sullivan CE. Neuroendocrine dysfunction in sleep apnea: reversal by continuous positive airways pressure therapy. J Clin Endocrinol Metab. 1989; 68:352–358. [PubMed: 2493027]

Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P. Testosterone replacement therapy with long-acting testosterone undecanoate improves sexual function and quality-of-life parameters vs. placebo in a population of men with type 2 diabetes. J Sex Med. 2013; 10:1612–1627. [PubMed: 23551886]

Hoyos CM, Killick R, Yee BJ, Grunstein RR, Liu PY. Effects of testosterone therapy on sleep and breathing in obese men with severe obstructive sleep apnoea: a randomized placebo-controlled trial. Clin Endocrinol (Oxf). 2012a; 77:599–607. [PubMed: 22512435]

Hoyos CM, Yee BJ, Phillips CL, Machan EA, Grunstein RR, Liu PY. Body compositional and cardiometabolic effects of testosterone therapy in obese men with severe obstructive sleep apnoea: a randomised placebo-controlled trial. Eur J Endocrinol. 2012b; 167:531–541. [PubMed: 22848006]

Isidori AM, Buvat J, Corona G, Goldstein I, Jannini EA, Lenzi A, Porst H, Salonia A, Traish AM, Maggi M. A critical analysis of the role of testosterone in erectile function: from pathophysiology to treatment-a systematic review. Eur Urol. 2014; 65:99–112. [PubMed: 24050791]

Jackson ML, Howard ME, Barnes M. Cognition and daytime functioning in sleep-related breathing disorders. Prog Brain Res. 2011; 190:53–68. [PubMed: 21531244]

Janowsky JS. The role of androgens in cognition and brain aging in men. Neuroscience. 2006; 138:1015–1020. [PubMed: 16310318]

Johns, MW. Appendix 1: The subjective measurement of excessive daytime sleepiness. In: Pandi-Perumal, SR.; Verster, J.; Monti, J.; Langer, S., editors. Sleep Disorders: Diagnosis and Therapeutics. CRC Press; Boca Ranton, FL, US: 2008. p. 643-657.

Kelleher S, Conway AJ, Handelsman DJ. Blood testosterone threshold for androgen deficiency symptoms. J Clin Endocrinol Metab. 2004; 89:3813–3817. [PubMed: 15292310]

Leproult R, Van Cauter E. Effect of 1 week of sleep restriction on testosterone levels in young healthy men. JAMA. 2011; 305:2173–2174. [PubMed: 21632481]

Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, Handelsman DJ. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. J Clin Endocrinol Metab. 2003; 88:3605–3613. [PubMed: 12915643]

Liu PY, Caterson ID, Grunstein RR, Handelsman DJ. Androgens, obesity, and sleep-disordered breathing in men. Endocrinol Metab Clin North Am. 2007; 36:349–363. [PubMed: 17543723]

Luboshitzky R, Aviv A, Hefetz A, Herer P, Shen-Orr Z, Lavie L, Lavie P. Decreased pituitary-gonadal secretion in men with obstructive sleep apnea. J Clin Endocrinol Metab. 2002; 87:3394–3398. [PubMed: 12107256]

Luboshitzky R, Lavie L, Shen-Orr Z, Lavie P. Pituitary-gonadal function in men with obstructive sleep apnea. The effect of continuous positive airways pressure treatment. Neuro Endocrinol Lett. 2003; 24:463–467. [PubMed: 15073577]

Quan SF, Chan CS, Dement WC, Gevins A, Goodwin JL, Gottlieb DJ, Green S, Guilleminault C, Hirshkowitz M, Hyde PR, Kay GG, Leary EB, Nichols DA, Schweitzer PK, Simon RD, Walsh JK, Kushida CA. The association between obstructive sleep apnea and neurocognitive performance–the Apnea Positive Pressure Long-term Efficacy Study (APPLES). Sleep. 2011; 34:303–314B. [PubMed: 21358847]

Rajfer J. Relationship between testosterone and erectile dysfunction. Rev Urol. 2000; 2:122–128. [PubMed: 16985751]

Reece M, Herbenick D, Schick V, Sanders SA, Dodge B, Fortenberry JD. Sexual behaviors, relationships, and perceived health among adult men in the United States: results from a national probability sample. J Sex Med. 2010; 7(Suppl 5):291–304. [PubMed: 21029386]

Saad F, Aversa A, Isidori AM, Zafalon L, Zitzmann M, Gooren L. Onset of effects of testosterone treatment and time span until maximum effects are achieved. Eur J Endocrinol. 2011; 165:675–685. [PubMed: 21753068]

Salmimies P, Kockott G, Pirke KM, Vogt HJ, Schill WB. Effects of testosterone replacement on sexual behavior in hypogonadal men. Arch Sex Behav. 1982; 11:345–353. [PubMed: 7149969]

Seftel AD, Mack RJ, Secrest AR, Smith TM. Restorative increases in serum testosterone levels are significantly correlated to improvements in sexual functioning. J Androl. 2004; 25:963–972. [PubMed: 15477371]

Shallice T. Specific impairments of planning. Philos Trans R Soc Lond B Biol Sci. 1982; 298:199–209. [PubMed: 6125971]

Stroop JR. Studies of interference in serial verbal reactions. J Exp Psychol. 1935; 18:643–662.

Svartberg J, Aasebo U, Hjalmarsen A, Sundsfjord J, Jorde R. Testosterone treatment improves body composition and sexual function in men with COPD, in a 6-month randomized controlled trial. Respir Med. 2004; 98:906–913. [PubMed: 15338805]

Travison TG, Morley JE, Araujo AB, O'Donnell AB, McKinlay JB. The relationship between libido and testosterone levels in aging men. J Clin Endocrinol Metab. 2006; 91:2509–2513. [PubMed: 16670164]

Vermeulen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab. 1999; 84:3666–3672. [PubMed: 10523012]

Wang C, Nieschlag E, Swerdloff RS, Behre H, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FC. ISA, ISSAM, EAU, EAA and ASA recommendations: investigation, treatment and monitoring of late-onset hypogonadism in males. Aging Male. 2009; 12:5–12. [PubMed: 18763169]

Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992; 30:473–483. [PubMed: 1593914]

Weaver TE, Laizner AM, Evans LK, Maislin G, Chugh DK, Lyon K, Smith PL, Schwartz AR, Redline S, Pack AI, Dinges DF. An instrument to measure functional status outcomes for disorders of excessive sleepiness. Sleep. 1997; 20:835–843. [PubMed: 9415942]

Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT. EMAS group. Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010; 363:123–135. [PubMed: 20554979]

Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea - A population health perspective. Am J Respir Crit Care Med. 2002; 165:1217–1239. [PubMed: 11991871]

Young LA, Neiss MB, Samuels MH, Roselli CE, Janowsky JS. Cognition is not modified by large but temporary changes in sex hormones in men. J Clin Endocrinol Metab. 2010; 95:280–288. [PubMed: 19880786]

Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006; 91:4335–4343. [PubMed: 16926258]

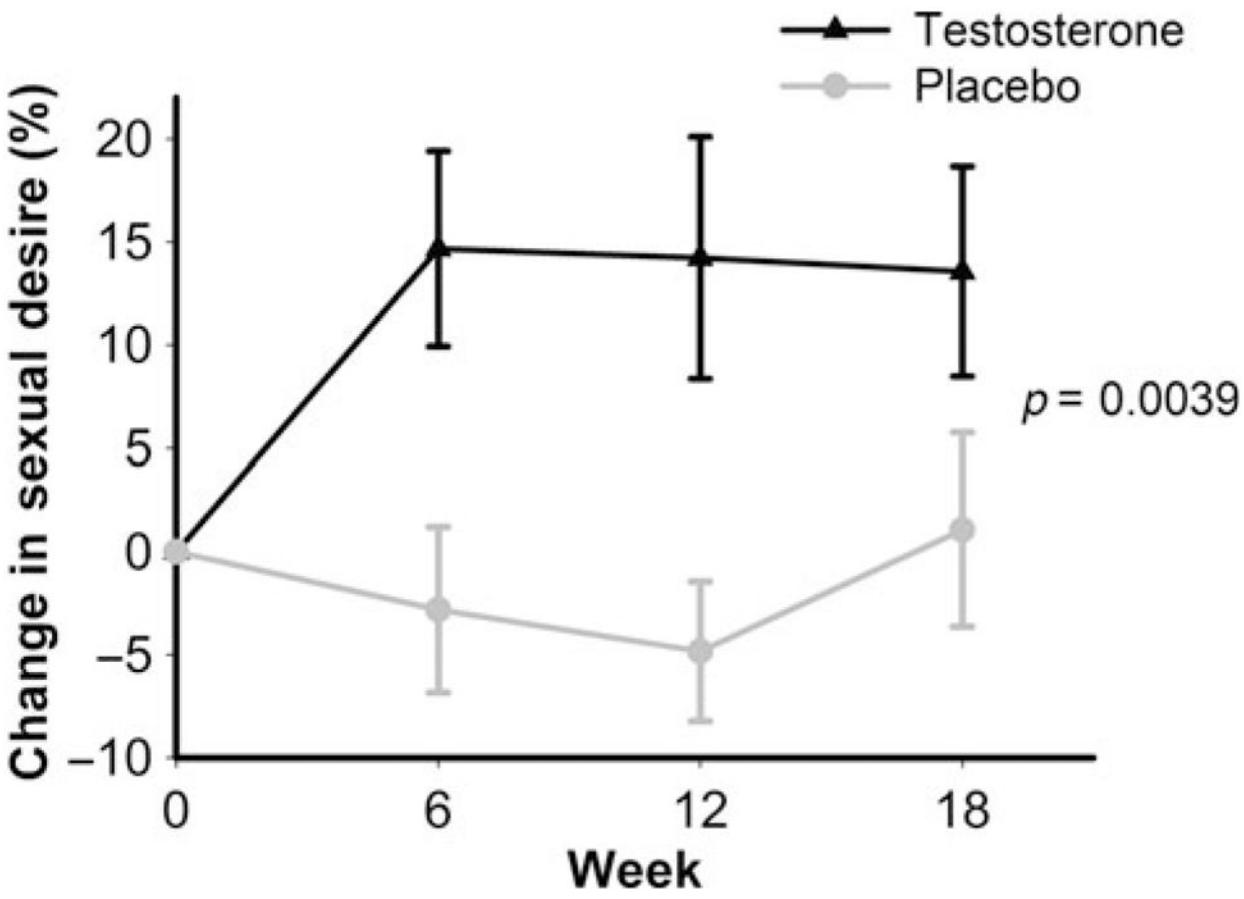

Figure 1.

Changes in sexual desire over time. Data are the mean change from baseline and standard error of the mean at each time point for men treated with testosterone (black line with triangles) or placebo (grey line with circles). The overall between group difference is indicated by the *p* value, determined by mixed model analysis.

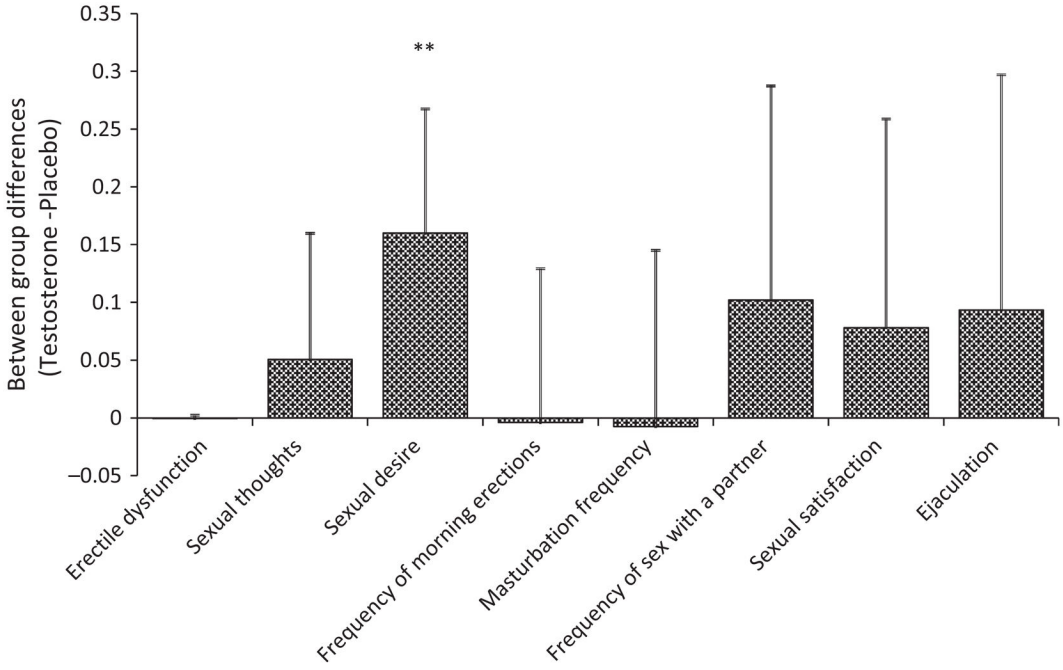

Figure 2.

Between-group difference in sexual function. Data are between-group difference (testosterone minus placebo) and 95% confidence intervals of the change from baseline averaged across time in sexual function domains. Significant differences are indicated by **.

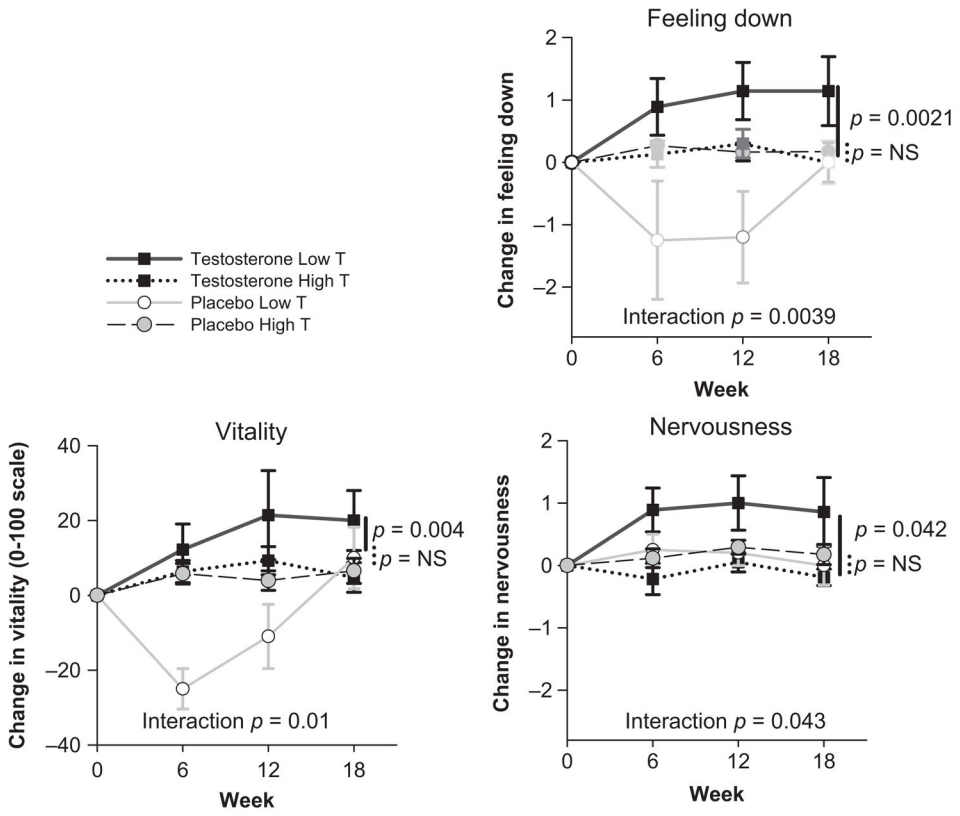

Figure 3.

Quality of life changes with testosterone for those with high (>8 nmol/L) and low (<8 nmol/L) baseline testosterone concentrations. Data are the mean change from baseline and standard error of the mean for men treated with testosterone (squares) and placebo (circles) in men with baseline testosterone below (solid lines) and above (dashed lines) 8 nmol/L. Data are shown for feeling down (upper right panel), vitality (lower left panel) and nervousness (lower right panel). The *p*-values for the overall interaction term are shown at the bottom of each panel, and for between-group differences on the right-hand side of each panel. The solid bar indicates significant differences between testosterone and placebo in those with baseline testosterone concentrations below 8 nmol/L are shown with the solid vertical line, and above 8 nmol/L with the dotted lines.

Table 1

Baseline participant characteristics

	Control (n = 34)	Testosterone (n = 33)	p value[a]
Age (years)	49 ± 1.6	48 ± 1.6	0.50
BMI (kg/m^2)	36.6 ± 4.9	34.9 ± 4.3	0.15
Total AHI (events/h)	25.6 (17.0, 40.1)	30.4 (18.8, 37.9)	0.86
ODI (events/h)	24.1 (14.8, 34.0)	19.0 (10.6, 29.8)	0.16
Minimum SpO_2 (%)	79.0 (74.0, 85.0)	85.0 (82.0, 87.0)	0.03
LH (U/L)[b]	3.1 (2.2, 3.6)	2.8 (2.2, 3.6)	0.41
FSH (U/L) [b]	4.5 ± 2.5	4.3 ± 3.7	0.76
Testosterone (nmol/L)[c]	11.8 ± 3.7	12.1 ± 5.2	0.77
Free testosterone (nmol/L)[b]	0.28 ± 0.07	0.29 ± 0.02	0.81
Sex hormone binding globulin (nM)[d]	20.4 (15.6, 28.8)	20.6 (16.5, 28.2)	0.81
Hypertension, n (%)	11 (32)	6 (18)	0.26
Hypertension medication, n (%)	10 (29)	5 (15)	0.24
Dyslipidemia, n (%)	6 (18)	4 (12)	0.51
Using PDE5 inhibitors (%)	0	0	
Type 2 diabetes, n (%)	6 (18)	0	0.02

Values are mean ± standard deviation or median (interquartile range) unless otherwise stated. BMI, body mass index; AHI, apnea hypopnea index; ODI, oxygen desaturation index; SpO_2, pulse oxygen saturation; LH, luteinizing hormone; FSH, follicle-stimulating hormone. Reference ranges: Testosterone 20–50 years: 6.0–29.0 nmol/L; >50 years: 5.0–30.0 nmol/L; free testosterone 80–370 pmol/L; sex hormone binding globulin 14.0–75.0 nmol/L.

[a] The p values were calculated by Student's t-test, Mann–Whitney U or Fisher's exact test where appropriate.

[b] Denotes data available in 66 participants.

[c] Denotes data available in 64 participants.

[d] Denotes data available in 65 participants.

Table 2

Baseline and overall changes in sexual function and neurocognitive function in testosterone and control groups

	Control group		Testosterone group		Mean between-group difference (95% CI)	*p*
	Baseline	**Overall change**	**Baseline**	**Overall change**		
Hormones and SHBG (*n* = 53)						
LH (U/L)	3.47 ± 1.54	0.17 (−0.43 to 0.76)	3.46 ± 2.31	−2.75 (−2.15 to −3.35)	−2.92 (−3.76 to −2.07)	<0.0001
FSH (U/L)	4.42 ± 2.67	0.13 (−0.60 to 0.86)	4.41 ± 3.94	−3.25 (−2.52 to −3.99)	−3.38 (−4.42 to −2.35)	<0.0001
Testosterone (nmol/L)	11.96 ± 3.90	0.94 (−0.49 to 2.37)	12.24 ± 5.60	6.43 (4.95 to 7.91)	5.49 (3.43 to 7.55)	<0.0001
Free testosterone[a] (nmol/L)	0.28 ± 0.07	0.004 (−0.03 to 0.04)	0.29 ± 0.12	0.11 (0.07 to 0.15)	0.11 (0.06 to 0.16)	<0.0001
Sex hormone binding globulin (nM)	23.13 ± 8.54	1.89 (0.58 to 3.18)	22.23 ± 8.28	0.39 (−0.97 to 1.74)	−1.49 (−3.37 to 0.39)	0.12
Sexual function (*n* = 56)						
Sexual thoughts (scale 0–1)	0.72 ± 0.29	−0.0061 (−0.08 to 0.07)	0.72 ± 0.29	−0.057 (−0.13 to 0.02)	0.051 (−0.058 to 0.16)	0.36
Sexual desire (scale 0–1)	0.69 ± 0.27	0.02 (−0.054 to 0.096)	0.63 ± 0.27	−0.14 (−0.22 to 0.06)	0.16 (0.05 to 0.27)	0.004
Frequency of morning erections (scale 0–1)	0.46 ± 0.33	−0.073 (−0.17 to 0.02)	0.55 ± 0.34	−0.069 (−0.16 to 0.03)	−0.0039 (−0.14 to 0.13)	0.95
Masturbation frequency (scale 0–1)	0.20 ± 0.30	−0.066 (−0.17 to 0.04)	0.34 ± 0.36	−0.058 (−0.17 to 0.051)	0.0073 (−0.16 to 0.15)	0.92
Frequency of sex with a partner (scale 0–1)	0.53 ± 0.45	0.038 (−0.092 to 0.17)	0.58 ± 0.41	−0.064 (−0.20 to 0.068)	0.10 (−0.08 to 0.29)	0.27
Sexual satisfaction (scale 0–1)	0.58 ± 0.40	−0.01. (−0.14 to 0.11)	0.64 ± 0.38	−0.09 (−0.22 to 0.04)	0.078 (−0.10 to 0.26)	0.39
Ejaculation (scale 0–1)	0.71 ± 0.43	−0.018 (−0.16 to 0.12)	0.67 ± 0.44	−0.11 (−0.26 to 0.03)	0.093 (−0.11 to 0.30)	0.36
Erectile dysfunction (scale 0–5)	1.86 ± 0.89	0.16 (−0.04 to 0.35)	1.68 ± 0.82	0.19 (−0.0037 to 0.39)	−0.03 (−0.30 to 0.24)	0.80
Tower of London (*n* = 49)						
Number of errors	0.3 ± 0.2	−0.1 (−0.1 to 0.0)	0.2 ± 0.1	−0.1 (−0.1 to 0.0)	0.0 (−0.1 to 0.1)	0.98
Number of missed goals	4.8 ± 3.9	−1.4 (−2.5 to −0.2)	4.0 ± 3.1	−1.3 (−2.5 to −0.1)	0.1 (−1.6 to 1.7)	0.92
Psychomotor vigilance task (*n* = 42)						
Reaction time (msec)	274.2 ± 54.1	−9.0 (−23.1 to 5.1)	275.9 ± 47.4	−12.7 (−26.2 to 0.7)	−3.7 (−23.2 to 15.8)	0.70
Stroop test (*n* = 47)						
Number of text correct (%)	93.1 ± 21.2	5.6 (−0.9 to 12.0)	96.4 ± 11.8	0.1 (−6.6 to 6.6)	−5.5 (−14.8 to 3.8)	0.24
Number of color correct (%)	98.2 ± 3.7	−11.5 (−20.7 to 2.4)	93.7 ± 19.1	−4.1 (−13.5 to 5.3)	7.4 (−5.7 to 20.6)	0.26

Baseline data are raw means ± standard deviation; overall mean change from baseline (95% confidence intervals) in control and testosterone groups, respectively; between-group differences (testosterone − control). Overall changes, between-group differences and *p*-value determined by mixed model analysis. Baseline data are presented for completed participants. CI, confidence interval; LH, luteinizing hormone; FSH, follicle-stimulating hormone.

[a]Denotes data available in 50 completed participants.