Testosterone Deficiency and Sleep Apnea

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KEYWORDS

• Obstructive sleep apnea • Testosterone deficiency • Sexual dysfunction
• Continuous positive airway pressure

KEY POINTS

- Obstructive sleep apnea (OSA) is associated with altered pituitary–gonadal function.
- Serum testosterone (T) has been shown to be lower in men with OSA.
- T supplementation may alter ventilatory responses and reduce sensitivity to hypercapnea.
- OSA may be a risk factor for erectile and sexual dysfunction in men.
- Treatment of OSA may help improve hypogonadism and sexual function.

INTRODUCTION

Obstructive sleep apnea (OSA) is a common condition among middle-aged men, affecting approximately 25% of men over the age of 40 (apnea hypopnea index [AHI] >5).[1] When looking at more subtle divisions of OSA severity, 18% of men in this age group still fall within the mild category, at AHI greater than 10, and 11% have at least moderate disease, with AHI greater than 15. This disorder is characterized by repetitive collapse of the airway during sleep, resulting in oxygen desaturation and sleep fragmentation. Observational studies have shown that OSA is a risk factor for cardiovascular morbidity, including hypertension, coronary heart disease, and stroke.[2–4] Sleep-disordered breathing has also been associated with altered pituitary–gonadal function. This article discusses the relationship between OSA and testosterone (T) deficiency.

Studies evaluating the relationship between T and sleep date back to the 1970s.[5–7] One of the earlier studies measured T and luteinizing hormone (LH) every 20 minutes for 24 hours in 9 pubertal boys and 3 sexually mature young men, and found that T levels fluctuated over the course of the day, with pubertal boys showing an increase in LH and T secretion during sleep. When the sleep–wake cycle was reversed, this pattern held true. However, this effect was not seen in sexually mature men. Another study evaluated T levels in men aged 22 to 32 years after night sleep and daytime sleep, and found an increase in T levels during any period of sleep and a decrease during waking hours, independent of circadian timing.[8] These studies suggest that LH-T augmentation during sleep is an important component of normal male physiology.

LOW TESTOSTERONE AND SLEEP APNEA: ROLES OF AGE, BODY MASS INDEX, AND SEVERITY OF SLEEP APNEA

Serum T has been shown to be lower in men with OSA.[9] Multiple studies describe a negative correlation between polysomnographic parameters—AHI, oxygen desaturation index (ODI), and nadir oxygen saturation - and testosterone levels.[10,11] A study by Luboshitzky and colleagues, measuring LH and T between 7 p.m. and 7 a.m. in obese men with OSA, obese men without OSA, and lean healthy men, found LH and T to be significantly lower in obese men with OSA compared with lean controls. Furthermore, both men with

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OSA and middle-aged controls had less pulsatile T release and reduced LH pulse amplitude, suggesting that, beyond the presence of OSA, obesity and age also play a role in androgen secretion.[12]

LOW TESTOSTERONE AND SLEEP APNEA: ROLE OF FATIGUE

Fatigue is a common reported symptom in OSA, even in the absence of daytime sleepiness.[13] Bercea and colleagues investigated the relationship between fatigue, OSA, and T levels in 2 groups consisting of OSA patients and age- and body mass index (BMI)-matched controls without OSA. In addition to lower serum testosterone, severe OSA patients also had more general fatigue, physical fatigue, mental fatigue, and reduced activity. In multivariate analyses, T level was the only independent predictor of physical fatigue and reduced activity in the OSA group. Of note, nadir oxygen saturation was not a significant predictor of fatigue. This study suggests that T deficiency in men with OSA has multiple health consequences, and fatigue may be an important factor affecting quality of life in this cohort.[14]

EFFECT OF TESTOSTERONE SUPPLEMENTATION ON OBSTRUCTIVE SLEEP APNEA

Untreated OSA has been considered a contraindication to T therapy, as it is believed that T replacement therapy (TRT) can worsen sleep apnea. Several studies have investigated the role of T administration in OSA. A case study by Cistulli and colleagues[15] reported that administration of high-dose T to a 13-year-old boy exacerbated OSA due to neuromuscular collapse of upper airway during sleep. Schneider and colleagues[16] found an increase in the number of apneas and hypopneas and a corresponding rise in AHI following androgen administration to hypogonadal males. These changes were noted without significant changes in upper airway dimensions or alterations in sleep stage distribution.

Matsumoto and colleagues[17] evaluated the effect of 6 weeks of biweekly 200 mg intramuscular T enanthate injections on hypoxic and hypercapnic ventilatory drive (ie, increase in ventilation induced by hypoxia or hypercapnea) in 5 hypogonadal men. Hypoxic ventilatory drive decreased significantly, while hypercapnic ventilatory drive did not. OSA developed in 1 subject and worsened in another. Both these patients showed a decrease in oxygen saturation, development of cardiac dysrhythmias during sleep, and an increase in hematocrit. On retrospective review of another group of elderly hypogonadal men with 2-year follow-up, a significant increase in hematocrit was seen, with 24% of men developing polycythemia (hematocrit [Hct] >52%) requiring phlebotomy or temporary cessation of testosterone therapy. No significant change in sleep-disordered breathing was reported, however.[18]

In a larger, randomized, placebo-controlled, cross-over trial of short-term high-dose T therapy, otherwise healthy participants with baseline T levels less than 450 ng/dL were given weekly injections of T (500 mg, 250 mg, 250 mg) and underwent polysomnographic testing and assessment of anthropometrics and airway bioimpedance. T treatment reduced rapid eye movement (REM) and non-REM (NREM) sleep by approximately 1 hour, although the proportion of time spent in each stage did not change significantly. RDI was increased by approximately 7 events per hour, and duration of hypoxemia was prolonged by T treatment. Interestingly, no significant change was seen in upper airway caliber, measured by awake acoustic reflectometry, or in neck and abdominal circumference. Rather, there was a reduction in serum leptin levels and adiposity, pointing to less pharyngeal fat deposition as a mechanism for the change in respiratory parameters.[19]

In a subsequent study, the same group studied obese adult men with OSA randomized to 3 intramuscular injections of T or placebo at 0, 6, and 12 weeks, and measured ventilatory chemoreflexes, including response to hypercapnea. They found a significant correlation between the hyperoxic carbon dioxide ventilatory recruitment threshold and increase in serum testosterone level at 6 weeks, indicating a dampened response to hypercapnea, along with a corresponding increase in time spent below oxygen saturation of 90% in sleep. A similar trend was seen for the ventilatory response in hypoxic conditions. This effect, however, did not persist on later measurements at week 18. The mechanism for this time-dependent difference in response remains to be better elucidated, although the findings suggest perhaps an effect of T on central chemoreceptors.[20]

MEN WITH OBSTRUCTIVE SLEEP APNEA AND SEXUAL DYSFUNCTION

There is growing evidence for an association between OSA and sexual dysfunction. Early observational data from Guilleminault and colleagues[21] indicated a high prevalence (48%) of erectile dysfunction (ED) in men with severe OSA. Margel and colleagues[22] also found a significant