

Obstructive Sleep Apnea and Testosterone Therapy

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ABSTRACT

Introduction: There is persistent speculation that testosterone therapy (TTh) may induce worsening of obstructive sleep apnea (OSA). As both the incidence of OSA and the use of TTh grow more prevalent, it is important to review the current evidence that supports or refutes this relationship.

Objectives: To review the current literature regarding the relationship between TTh and OSA.

Methods: A literature search was conducted to identify relevant studies. Search terms included “obstructive sleep apnea” and “testosterone replacement therapy.” Titles and abstracts were reviewed for relevance. References from identified articles were searched and included, if appropriate.

Results: The association between TTh and OSA was initially described in a 1978 case report of an individual with worsened nighttime apneas during testosterone administration, a trend seen again in subsequent small case series. In the 1990s, a large retrospective analysis and the first randomized controlled trial on the subject revealed no increased incidence of OSA in individuals on TTh. A randomized controlled trial conducted in 2012 provided a possible explanation to the previously reported discrepancies, describing a time-limited effect, wherein measures of OSA were elevated at seven weeks but were not significantly different at 18 weeks after initiation of TTh. A recent cohort study demonstrated an incidence of OSA in individuals on TTh of 16.5% compared with 12.7% in controls. TTh is thought to affect OSA in several ways. Theories that the anabolic effects of testosterone may decrease airway patency or that testosterone alters sleep architecture have been largely disproven. More likely, testosterone plays a role in altering neural response pathways to hypoxemia.

Conclusions: TTh likely plays a small role in exacerbating or inducing changes in OSA that may be time limited in nature. Clinicians may choose to exercise caution in prescribing TTh to individuals suffering from severe OSA.

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INTRODUCTION

Obstructive sleep apnea (OSA) is marked by reduced rapid eye movement (REM) sleep and deep sleep time, increased night awakenings, and reduced sleep efficiency.^{1,2} The disease is estimated to be present in 13–31% of males, with higher rates observed in the elderly (90% of males aged 65–80 years) and the obese (88.8% of men with a BMI > 30 kg/m²).^{3,4}

Testosterone levels are intimately tied to the sleep cycle, with multiple studies demonstrating that testosterone levels increase during sleep and decrease during waking in a log linear fashion.^{5,6} Testosterone levels peak at the time of first REM sleep, so that disrupted sleep preventing the initiation of REM sleep results in a delay in testosterone's peak concentration.⁷ In a paradoxical effect, OSA is associated with reduced serum testosterone levels, whereas testosterone therapy (TTh) may induce or exacerbate OSA.^{8–13}

TTh is indicated for the treatment of patients with symptomatic testosterone deficiency.¹⁴ These symptoms include decreased libido, erectile dysfunction, loss of lean muscle mass, fatigue, and depressed mood.^{15–17} TTh improves erectile function, increases sexual desire, strength, lean mass, and even lipid profiles.^{18–22} TTh is estimated to decrease body weight by 13.57 ± 0.37% over 5 years.²³ In addition, TTh can significantly improve scores on measures of depression and overall quality of life.^{24–26} Questions have been raised about testosterone's overall

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safety profile, including the potential for increased cardiovascular risk and risk of thromboembolism.^{20,27} This review summarizes the evidence and theory surrounding the risk of OSA in men on TTh.

METHODS

A systematic review of the literature was conducted to identify relevant studies examining the effects of TTh on OSA. The PubMed and [ClinicalTrials.gov](https://www.clinicaltrials.gov/) databases were searched using the following combinations of MeSH terms: obstructive sleep apnea and testosterone replacement therapy, obstructive sleep apnea and androgen replacement therapy, obstructive sleep apnea and hypogonadism. The literature search was limited to English publications or publications translated into English, and databases were searched from dates of their inception through June 2019. Studies gathering primary data, retrospective analyses, systematic reviews, and meta-analyses were included. There were no applicable active trials from [ClinicalTrials.gov](https://www.clinicaltrials.gov/). Unpublished material was excluded. Articles and abstracts were reviewed in an unblinded manner to determine eligibility and relevance. References from identified articles were also explored and included, if appropriate.

The Role of Obesity in the Link Between Testosterone Therapy and Obstructive Sleep Apnea

In considering the relationship between OSA and TTh, it is first important to address the role of obesity as a potential confounding factor. Obesity is strongly linked to both hypogonadism and OSA.²⁸ A well-established bidirectional relationship exists between testosterone levels and obesity. In the Hypogonadism in Men (HIM) study, Mulligan et al found that 52.4% of obese men were testosterone deficient.²⁹ This effect may be mediated by suppression of the hypothalamic-pituitary-gonadal (HPG) axis in obese individuals. Adipocytes express high levels of aromatase, which mediates conversion of testosterone to estrogen. Increased estrogen levels negatively feed back to the hypothalamus, decreasing gonadotropin-releasing hormone (GnRH), and ultimately luteinizing hormone (LH) release, resulting in decreased gonadal testosterone production.³⁰ Weight loss, through diet and exercise and bariatric surgery, can correlate with increases in testosterone levels.²⁸

Importantly, a reverse relationship has also been shown, wherein testosterone levels affect body mass composition. Studies have shown that while testosterone does not change overall body weight, it does on the whole reduce fat mass while increasing lean muscle mass. TTh has also been linked to reduced waist circumference, an important contributor to the metabolic syndrome.^{23,31}

Obesity, across multiple studies, has been identified as an important risk factor for OSA.^{32,33} Indeed, the Wisconsin Sleep Cohort showed a 6-fold increase in the odds of developing OSA with a 10% weight gain.³⁴ Rather than BMI alone, visceral fat

distribution is important in OSA risk. Waist and neck circumference correlates better than BMI with OSA severity.³⁵ The risk of OSA is also higher with larger tongue volume, lateral pharyngeal wall volume, and total upper airway soft tissue volume.³⁶

Polycythemia in Men on Testosterone Therapy With Obstructive Sleep Apnea

Polycythemia presents a potential additional concern for men on TTh. A recent literature review demonstrated that men on TTh have a 315% greater chance of developing erythrocytosis and polycythemia than controls.³⁷ Increases in hemoglobin and hematocrit were observed with every type of testosterone formulation (intramuscular injection, oral, transdermal patch, topical gel, subcutaneous pellets, buccal), although the effect was most significant with intramuscular injections. An increased risk of venous thromboembolism was not linked to elevated hematocrit. OSA, given potential periods of nocturnal hypoxemia, can also contribute to erythrocytosis. However, multiple cohort studies have not observed an association between OSA and erythrocytosis.^{38–40} In a large retrospective multivariate analysis of 1,604 patients, erythrocytosis (defined as hematocrit > 51% in men) was uncommon (1.6%) in those with OSA.⁴¹ In addition, OSA severity was not associated with hematocrit. Nocturnal hypoxemia was, however, an independent predictor of erythrocytosis (odds ratio [OR] 1.8, $P = .021$), although only 34.2% of men with OSA had nocturnal hypoxemia. Testosterone therapy was observed to be a significant predictor of nocturnal hypoxemia (OR 2.3, $P = .002$). Given these findings, clinicians may choose to monitor more closely for erythrocytosis in patients with preexisting OSA being placed on TTh.

Does Testosterone Therapy Worsen OSA?

The effect of TTh on OSA has been debated since the first report of a possible association by Strumpf et al in 1978 and remains without clear consensus today.⁴² The literature examining this link has generally favored a negative effect of TTh on OSA, although more recent studies have suggested this effect is present but may be time limited ([Table 1](#)). Sandblom et al in 1983 treated a 126 kg individual with a lifelong history of snoring with 7 months of weekly TTh (200 mg intramuscular dose) followed by 3 months of TTh at the same dose and rate plus 5,000 IU human chorionic gonadotropin 3 times weekly.⁴³ The patient self-reported worsening sleep quality and daytime somnolence. These symptoms abated when the TTh was discontinued for 5 weeks and returned when TTh was restarted. The patient was obese at baseline but did not have self-reported symptoms of sleep apnea before TTh. The apneic index (number of episodes of apnea lasting for more than 10 seconds per hour of sleep) during each period of TTh was 26 and 40 (normal is less than 5), and returned to 1 six months after discontinuation of TTh, providing impetus for further investigation into the potential effects of TTh on sleep apnea. The same group built on

Table 1. Comparison of studies measuring effects of TTh on OSA

Author	Year	Treatment	Effect	Adverse events
Strumpf et al. ⁴²	1978	Unspecified TTh IM for unreported duration on 1 hypogonadal patient, repeated with depo testosterone for 4 months	Developed right ventricle failure and hypersomnolence, improved after 7 months off of TTh; moderate restrictive ventilatory defect, hypoventilation, blunted central response to CO ₂ on repeat	None reported
Sandblom et al. ⁴³	1983	Testosterone enanthate 200 mg weekly for 7 months + 5,000 IU HCG x 1 year in 1 hypogonadal patient	Worsened OSA (apneic index 26 and 40). Symptoms abated 5 weeks after therapy (apneic index 1) and recurred when restarting	Pedal edema
Matsumoto et al. ⁴⁴	1985	Testosterone enanthate 200 mg IM every 2 weeks for 6 weeks in 5 hypogonadal patients	Worsening OSA in one patient (AHI 22 to 48), new diagnosis of OSA in another	One subject developed rapid atrial fibrillation-flutter, one subject developed sinus bradycardia in association with OSA episodes, 2 subjects developed erythrocytosis
Millman et al. ⁴⁵	1985	Testosterone enanthate 250 mg weekly for unreported duration in 5 ESRD patients	No change in polysomnography 2 months after stopping TTh	None reported
Hajjar et al. ⁴⁶	1997	Testosterone enanthate or cypionate 200 mg IM every 2 weeks for unreported duration in 72 randomized hypogonadal patients	1 patient reported worsened OSA, most reported improved sleep	24% of subjects in the testosterone group developed polycythemia. Of subjects who discontinued, one discontinued due to gynecomastia and one due to sleep apnea.
Snyder et al. ⁴⁷	1999	Testosterone patch 6 mg/24 hours for 36 months randomized to 108 patients	1 patient in control and 1 in study group had worsened RDI	One subject developed prostate cancer
Liu et al. ⁴⁸	2003	Testosterone enanthate injections 500, 250, and 250 mg spaced 1 week apart with an 8-week washout before one repeat of the series randomized in 17 patients	1 hour less of sleep and reduced NREM, REM, and sleep efficiency in testosterone patients	One subject discontinued due to recurrence of long-standing cervical neck pain. 2 men had transient nipple tenderness.
Hoyos C, et al. ⁴⁹	2012	Testosterone undecanoate 1,000 mg IM every 6 weeks for 18 weeks randomized in 67 patients	Testosterone patients had 6.1% increase in nocturnal hypoxemia episodes and a worsened ODI by 10.3 events/hour	No discontinuation due to severe sleepiness or sleep-related problems
Cole et al. ⁵⁰	2018	Retrospective analysis of 3,422 hypogonadal patients on testosterone	2-year risk of OSA in men on testosterone 16.5%, compared to 12.7% in controls	N/A

these findings in a 1985 study of 5 hypogonadal men who received 6 weeks of testosterone enanthate 200 mg intramuscularly every 2 weeks.⁴⁴ The authors describe worsening of preexisting sleep apnea in one individual, whose apnea hypopnea index (AHI) increased from 22 to 48, and new onset sleep apnea in another (AHI increased from 3 to 10).

A series of studies during the decade following these early findings increasingly called into question the association between TTh and worsening OSA. In 1985, Millman et al reported on 5 hypogonadal men with preexisting OSA on hemodialysis receiving weekly testosterone enanthate 250 mg injections to stimulate erythropoiesis.⁴⁵ None of the 5 qualified as obese based on BMI. These individuals underwent polysomnography at baseline and 2 months, which revealed no change in the number of apneic or hypopneic episodes and no change in reported sleep quality. The mean total number of apneas and hypopneas per hour of sleep time was 52 ± 38 before TTh and 55 ± 38 after 2 months of TTh. A retrospective analysis by Hajjar et al in 1997 examined the overall safety profile of TTh, with 27 hypogonadal men receiving a 200 mg intramuscular dose of testosterone enanthate or cypionate every 2 weeks.⁴⁶ The BMI of control subjects was 26.4 ± 0.9 kg/m² while the BMI of study subjects was 27.4 ± 0.7 kg/m², a difference that was not significant. Although it was not a primary aim of the study and no formal sleep studies were performed, the authors observed that only 1 subject self-reported worsening sleep apnea, leading to his discontinuation of TTh. Most subjects, in fact, reported better sleep habits as part of an overall sensation of well-being while on TTh.

The first randomized controlled trial examining the relationship between TTh and OSA was conducted in 1999 by Snyder et al and involved 108 men randomized to wear a testosterone or placebo patch over 3 years, with OSA testing at 6, 12, 24, and 36 months.⁴⁷ The mean weight in the placebo group was 81.1 ± 11.2 kg and the mean weight in the treatment group was 82.7 ± 9.5 , which were not significantly different. The respiratory distress index (RDI), a composite of apneas, hypopneas, and

respiratory effort—related arousals, was measured in placebo and control groups. In the placebo group, the RDI was 3.6 ± 4.9 pretreatment and 4.0 ± 4.2 after 36 months of placebo. In the TTh group, the RDI was 5.2 ± 6.1 pretreatment and 7.5 ± 8.5 after 36 months of TTh. The change in RDI between control and study groups before and after treatment was not statistically different. Only one patient in the treatment group and one in the control group had increases in the RDI from normal (less than 5 events per hour) to abnormal (greater than 15 events per hour).

Several double-blinded, randomized controlled trials were subsequently undertaken, which once again spurred re-evaluation of the safety of TTh with regards to the risk of OSA. In a 2003 crossover study by Liu et al, 17 men were randomized to receive placebo injections or 3 intramuscular weekly testosterone ester injections of 500 mg, 250 mg, and 250 mg.⁴⁸ The authors reported 1 hour less of sleep per night in men on testosterone, as well as reduced time in nonrapid eye movement (NREM) sleep, REM sleep, and reduced sleep efficiency. Absolute hypoxemia (time spent at oxygen saturation less than 90%) increased by 5 minutes, with a relative hypoxemia increase of 2% of total time slept. Total RDI increased by 7 events per hour. Anthropometrically, subjects had an increase in total weight of about 2 kg during the study period, which was made up by a 3 kg increase in lean mass and a 1 kg reduction in fat mass. Study subjects underwent abdominal and neck circumference measurements and upper airway caliber measurement, which were unchanged in despite overall weight changes. Because the link between obesity and OSA is thought to be mediated by upper airway narrowing, the authors concluded that obesity did not play a role in observed breathing changes.

Building on this study of short-term, high-dose TTh, the same authors then studied longer-term doses.⁴⁹ In a double-blind, randomized, placebo-controlled trial, 67 obese (BMI > 30 kg/m²) men with preexisting OSA were treated with 1,000 mg IM testosterone undecanoate at 0, 6, and 12 weeks. This was the first study to treat men with severe OSA with TTh. Baseline BMI was not significantly different between groups, but the group receiving TTh had lower pretreatment waist circumference (115.7 ± 8.8 cm vs 120.7 ± 11.1 cm; $P = .04$). Both treatment and placebo groups simultaneously completed a weight loss program; weight decreased significantly over time in both groups and amount of weight lost did not significantly differ between the groups at any point. Polysomnography was performed at 0, 7, and 18 weeks. At 7 weeks, individuals on TTh had a 6.1% increase (95% confidence interval [CI], 1.5–10.6; $P = .01$) in total sleep time spent in hypoxemia episodes and a worsened oxygen desaturation index (ODI) by 10.3 events per hour (95% CI, 0.8–19.8 events/h; $P = .03$). Changes in AHI did not meet statistical significance. Interestingly, no differences between groups in nocturnal hypoxemia (2.9, -1.9 – 7.7% ; $P = .23$) or ODI (4.5, -5.4 to 14.4 events/h; $P = .36$) were observed at 18 weeks, leading the authors to conclude that TTh mildly worsens OSA, but only in a time-limited manner.

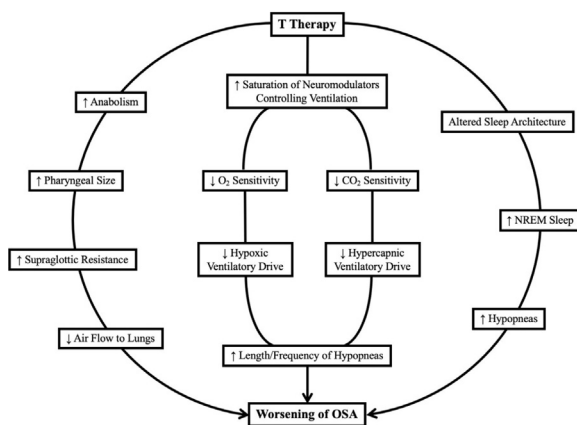


Figure 1. Possible pathophysiologic mechanisms by which testosterone therapy affects obstructive sleep apnea (OSA).

Because of the weight loss component of this study, it is important to assess whether this is a confounding factor. At 18 weeks, the TTh group had lost ~1 kg and the placebo group had lost ~3 kgs. Peppard et al showed that even a 5% reduction in weight leads to an average 14% reduction in the AHI, although the men in the present study lost less than 5% of their starting weight. It is possible that increased weight loss between 7 weeks to 18 weeks could have played a role in the elimination of this distinction if more obese men are predisposed to developing OSA with TTh at a higher rate than nonobese men. Future studies are needed to determine if such a relationship exists. Even so, it is difficult to assess the role that weight changes over time.

In 2018, Cole et al completed the first large population-based study to evaluate the risk of OSA among TTh users.⁵⁰ In a retrospective matched cohort study of 3,422 male U.S. military members, retirees, and dependents on TTh for hypogonadism, the authors found a 2-year risk of OSA in men on TTh of 16.5% (95% CI, 15.1–18.1; $P < .001$), compared to 12.7% (95% CI, 11.4–14.1; $P < .001$) in controls. The authors caution that they were unable to assess TTh dose or how OSA was diagnosed (eg, specific polysomnography criteria vs clinical diagnosis) and that the experiences in a military population may not be generalizable to the civilian population. Furthermore, the authors relied on diagnostic codes for obesity to control for it but did not have access to BMI values, which may have introduced bias.

Taken together, current evidence suggests that short-term, high-dose TTh may worsen OSA. For men on longer-term TTh, disordered breathing patterns may normalize over time, rather than worsen. However, the role that obesity plays in this relationship remains unclear. A large population-based study indicates that in practice, the overall incidence of OSA may be slightly increased in men on TTh. The effects described are fairly small but may be significant enough to affect individuals with severe OSA or risk factors for OSA. Health care practitioners should consider screening for OSA as one element of evaluating the appropriateness of TTh in a given patient.

How Does Testosterone Therapy Impact Obstructive Sleep Apnea?

Given the possible role of TTh in exacerbating OSA, considerable investigation has been done to examine potential mechanisms (Figure 1). One possible way in which TTh worsens OSA is through morphological change to the airway. Given the anabolic effects of testosterone, a reduction in the patency of the upper airway could predispose individuals to apneas during sleep. Schneider et al tested this theory in 4 hypogonadal males on TTh with biweekly injections of testosterone enanthate for 90 days.⁵¹ The authors observed no significant change in upper airway patency by CT scan and no change in supraglottic airflow resistance. Mean supraglottic resistance was 7.7 ± 2.2 cmH₂O·l⁻¹·s off TTh and 6.2 ± 0.7 cmH₂O·l⁻¹·s on TTh. Mean pharyngeal airway size was 184.5 ± 50.1 mm off TTh and 199.5 ± 46.3 mm on TTh. Similarly, Liu et al, in a randomized

controlled trial of testosterone administration in 17 men, observed no changes in direct measurement of upper airway caliber by acoustic reflectometry and no changes in neck circumference.⁴⁸ An additional factor undermining the potential for airway patency changes is that alterations in sleep duration and hypoxemic sleep time were observed 2–4 days after IM testosterone administration, a duration of therapy too short for meaningful anabolic soft tissue growth to occur.

Another potential mechanism by which TTh may exacerbate OSA is through changes in sleep architecture, as increased time spent in REM sleep could yield more disordered breathing. Matsumoto et al, in a study of TTh in 5 hypogonadal men, showed significant increases in the amount of time spent in REM sleep after addition of TTh, from a mean of $14 \pm 3\%$ to $22 \pm 2\%$ ($P < .001$) of total time sleeping; however, the majority of apneas occurred during non-REM (NREM) sleep.⁴⁴ Liu et al saw no changes in the proportion of time spent in NREM and REM sleep, and likewise saw that the majority of apneas and hypopneas occurred during NREM sleep.⁴⁸ Schneider et al saw no changes in sleep stages on and off TTh in 11 hypogonadal males.⁵¹ Specifically, mean percentage of total sleep time spent in REM sleep off TTh was $15.2\% \pm 2.4$ and on TTh was $16.2\% \pm 1.2$ ($P < .05$). Similarly, Hoyos et al also observed no significant alterations in sleep architecture between subjects on TTh and controls.⁴⁹ Individuals receiving placebo had a 0.47% mean increase in percentage of total sleep time spent in REM sleep; individuals receiving TTh had a 0.49% increase in the same value (mean difference of -0.16 , confidence interval -3.32 to 3.01 ; $P = .92$). These results suggest that changes in sleep stage composition do not play a significant role in TTh's exacerbation of sleep disordered breathing.

A more promising theory centers on the role of androgens in neural response pathways to hypoxemia. The administration of testosterone has variable effects on ventilatory chemoresponsiveness. This has been assessed across multiple studies, albeit without a single unifying conclusion. In 5 hypogonadal men receiving 200 mg testosterone enanthate every 2 weeks, Matsumoto et al observed a decrease in the hypoxic ventilatory drive (change in ventilation in response to low oxygen levels) from 158 ± 39 off TTh to 88 ± 19 on TTh ($P < .05$).^{44,52} Hypercapnic ventilatory drive (change in ventilation in response to high carbon dioxide levels) was not significantly different. White et al published conflicting results in the same year, finding that in 12 hypogonadal males receiving a single 200 or 400 mg IM testosterone dose, hypoxic ventilatory drive increased from 122 ± 23 to 176 ± 28 ($P < .01$) and hypercapnic ventilatory drive was not significantly changed.⁵³ Minute ventilation and metabolic rate were both increased [from 8.41 L/min ± 0.78 to 9.91 L/min ± 0.75 ($P < .05$) and from 248 mL/min ± 15 to 276 mL/min ± 18 ($P < .05$), respectively]. In a study conducted in neutered male cats, testosterone administration increased hypoxic and hypercapnic ventilatory responsiveness.⁵⁴ The hypoxic sensitivity of the carotid body was also increased, suggesting that testosterone may act both centrally and peripherally to alter ventilation.

Mateika et al showed in 2004 that androgens may exert changes on ventilation during both wakefulness and sleep. The authors suppressed testosterone in 11 men using the anti-androgen leuprolide acetate and demonstrated a decreased ventilatory recruitment threshold (41.05 ± 0.77 vs. 39.40 ± 0.83 Torr; $P = .01$) and decreased CO_2 chemosensitivity (4.82 ± 0.61 vs. 7.17 ± 1.20 l min^{-1} Torr $^{-1}$; $P = .02$) during wakefulness, as well as a decreased apneic threshold in 5 subjects during NREM sleep (42.1 ± 0.6 versus 39.6 ± 0.6 Torr, $P = .002$).⁵⁵ Killick et al extended previous work by showing that there may be a time-limited nature to testosterone's effects. In a study of 21 men with OSA randomized to testosterone or placebo, positive correlations between change in serum testosterone and change in the carbon dioxide ventilatory recruitment threshold (r (Pearson's correlation) = 0.55, $P = .03$) and between carbon dioxide ventilatory recruitment threshold and time spent with oxygen saturations less than 90% during sleep ($r = 0.57$, $P = .03$) were observed at 6-7 weeks, but resolved by 18 weeks of TTh. These findings suggest that testosterone may alter chemoreceptor stimulation thresholds or the ventilatory response to chemoreceptor stimulation in a way that decreases breathing stability. Future studies are needed to resolve currently conflicting evidence as to the mechanisms mediating this change.

Of note, obesity itself may cause aberrant ventilatory response, which could account for variable findings previously described given the high prevalence of obesity in OSA patients. Similar to the case of androgens, however, the direction of alteration is not consistent across studies. Burki et al demonstrated increased ventilatory responsiveness to hypoxia but decreased ventilatory responsiveness to hypercapnia in morbidly obese subjects.⁵⁶ Chapman et al, by contrast have shown a positive correlation between BMI and hypercapnic ventilatory response in obese patients being evaluated for gastropasty.⁵⁷ Larger powered studies are needed to fully assess the effect of obesity as a potential confounding variable in measurements of ventilatory response.

CONCLUSION

As TTh is increasingly used, it is important to understand its potential adverse effects.⁵⁸ The idea that TTh may exacerbate OSA dates back more than 40 years. For several decades, the association was explored using only case studies or small uncontrolled case series, which suggested that TTh worsened OSA. As larger cohort studies and RCTs became available, this relationship has been questioned. The best current evidence suggests that short-term, high-dose testosterone administration mildly worsens OSA. Longer-term TTh in subjects undergoing concomitant weight loss was shown to mildly worsen OSA but only initially. By 18 weeks, patients demonstrated return to baseline levels of OSA risk. These results suggest that TTh's role in exacerbating OSA is small and may be time limited. However, it is also possible that

weight loss acted as a confounding factor. Additional studies are needed to determine if men who are more obese at baseline have a higher risk of developing OSA with TTh than nonobese men. Why testosterone would have a time-dependent effect, however, remains unanswered. Regarding the mechanisms by which TTh may worsen OSA, anatomic TTh-induced airway changes and altered sleep stage architecture have been largely refuted. The mechanism of action is more likely related to altered hypoxic and hypercapnic ventilatory response with testosterone administration, though work is still needed to resolve inconsistencies in currently available studies. Until these questions are more fully understood, clinicians may choose to exercise caution in prescribing TTh to individuals with severe, untreated OSA.

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Conflicts of Interest: Dr Pastuszak is an advisor, consultant, and speaker in Endo Pharmaceuticals and receives research support from Endo Pharmaceuticals; an advisor in Boston Scientific; an advisor in Antares Pharmaceuticals; a speaker in Bayer AG; a founder and has a leadership role in Woven Health; has a leadership role in Vault Health; an advisor in Allotrope Medical. Dr Lipshultz is a consultant in AbbVie; a speaker in Boston Scientific; a consultant in Aytu Bioscience; a speaker/consultant in Endo Pharmaceuticals; a consultant in Lipocine.

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