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TESTOSTERONE REPLACEMENT IN HYPOGONADAL MEN: EFFECTS ON OBSTRUCTIVE SLEEP APNOEA, RESPIRATORY DRIVES, AND SLEEP

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SUMMARY

The obstructive sleep apnoea syndrome occurs predominantly in men. To determine the effect of testosterone on ventilatory function and whether testosterone may play a role in the development of obstructive apnoea, we performed waking ventilatory drive studies and sleep studies in five hypogonadal men. These androgen-deficient subjects were studied both while receiving no treatment and after six weeks of testosterone replacement therapy (testosterone oenanthate 200 mg i.m. every 2 weeks). Hypoxic ventilatory drive decreased significantly, from 158 ± 39 (mean $\pm$ SEM) off testosterone to 88 ± 19 on testosterone therapy ($P < 0{\cdot}05$). Hypercapnoeic ventilatory drive did not change significantly on testosterone. Obstructive sleep apnoea developed in one man and markedly worsened in another man in association with testosterone administration. Both of these subjects also exhibited marked decreases in oxygen saturation with the development of cardiac dysrhythmias during sleep and large increases in haematocrit. The remaining three hypogonadal men did not demonstrate significant sleep apnoea either on or off testosterone. The percentage of sleep time spent in REM sleep increased from $14 \pm 3\%$ to $22 \pm 2\%$ when the men were receiving testosterone ($P < 0{\cdot}01$), but the episodes of sleep apnoea tended to occur during non-REM sleep. We conclude that in some hypogonadal men, replacement dosages of testosterone may affect ventilatory drives and induce or worsen obstructive sleep apnoea. The obstructive sleep apnoea syndrome is a potential complication of testosterone therapy. These results suggest that androgen levels present in normal man may play an important role in the pathogenesis of obstructive sleep apnoea.

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Obstructive sleep apnoea is characterized by repeated episodes of upper airway occlusion during sleep which may result in diminished arterial oxygen saturation, severe cardiovascular disturbances and disabling sleep disruption (Guilleminault *et al.*, 1976). Since obstructive apnoea occurs predominantly in men and postmenopausal women, and rarely occurs in premenopausal women, several investigators have proposed that sex steroid hormones may play a role in the pathogenesis of this syndrome (Guilleminault *et al.*, 1978; Block *et al.*, 1979). Progesterone is present in relatively higher concentrations in premenopausal women compared to men and postmenopausal women (Judd & Korenman, 1982) and is known to stimulate waking ventilatory drives (Skatrud *et al.*, 1978). These observations have led to the speculation that progesterone may exert a protective effect on the development of sleep apnoea. However this steroid, even when administered in pharmacological dosages, is usually ineffective (Hensley *et al.*, 1980; Block *et al.*, 1981).

We recently reported the development of the obstructive sleep apnoea syndrome on two separate occasions in association with high dosage testosterone administration in an obese but otherwise normal man (Sandblom *et al.*, 1983). The syndrome remitted each time that testosterone was discontinued. Exogenous testosterone administration is commonly used in replacement therapy of androgen-deficient, hypogonadal men. Although this therapy is generally benign, excessive erythrocytosis, hypertension, peripheral oedema, and even cor pulmonale have been reported to complicate testosterone therapy (Strumpf *et al.*, 1978; Bardin & Paulsen, 1981). These findings also occur as a result of repetitive episodes of obstructive apnoea during sleep (Guilleminault *et al.*, 1976). In the present study, we examined the effect of testosterone replacement therapy in hypogonadal men on awake and sleeping ventilatory function. Five hypogonadal men underwent awake ventilatory drive studies and sleep studies before and after a six-week period of testosterone treatment.

METHODS

Subjects

Five androgen-deficient men, aged 24–71 years, were studied. Informed consent was obtained from each subject. Subject 1 was a 71-year-old white male with Klinefelter's syndrome, hypertension, and compensated, asymptomatic congestive heart failure and atrial fibrillation. Subject 2 was a 57-year-old white male with idiopathic hypogonadotropic hypogonadism and hypertension. This subject had no history or clinical evidence of congestive heart failure and was not on beta-adrenergic blocking agents. Subject 3 was a 54-year-old white male with idiopathic panhypopituitarism and diabetes insipidus. Subject 4 was a 24-year-old white male with Klinefelter's syndrome. Subject 5 was a 67-year-old black male with primary hypogonadism following successful chemotherapy and radiation for Hodgkin's disease.

All were overweight (average 87 ± 2 kg mean $\pm$ SEM), approximately 122% of ideal body weight according to 1983 Metropolitan Life Insurance Company weight tables. Off testosterone therapy, these hypogonadal men all exhibited clinical symptoms of androgen deficiency. Subjects were otherwise in good health and none had a history of smoking, chronic respiratory disease, drug abuse or excessive alcohol intake. All subjects gave a history of snoring during sleep. Examination of the upper airway was normal in all five men.

Protocol

The experimental protocol was reviewed and approved by the Human Subjects Review Committee of the University of Washington. All subjects were studied on two occasions, once 6 weeks after starting testosterone replacement therapy (testosterone oenanthate 200 mg i.m. every 2 weeks) and again, 6 weeks after stopping testosterone treatment. Subjects 1, 4, and 5 were studied off testosterone first, while Subjects 2 and 3 were studied on testosterone first. At the end of each study period, sleep studies and awake pulmonary function and ventilatory drive studies were performed by investigators who were blinded to each subject's testosterone regimen. Subjects on testosterone replacement treatment were studied two days after their last testosterone oenanthate injection. Otherwise, medications remained unchanged throughout the study.

Polysomnography was performed during an overnight study, after one night of adaptation to the sleep laboratory. Simultaneous recordings of electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, airflow at the nose and mouth, chest and abdominal impedence plethysmograms, oxygen saturation by ear oximetry, and end-tidal carbon dioxide were obtained. Monitoring equipment was in a different room from that in which the subjects slept. All data were processed and analysed in 30 s intervals. Sleep stages were scored according to the criteria of Rechtschaffen & Kales (1973) and episodes of apnoea were defined according to the criteria of Guilleminault *et al.* (1976). An episode of obstructive apnoea was defined as cessation of airflow for longer than 10 s with continued chest and abdominal movements. Hypopnoea was defined as a decrease in airflow to one-third of its basal value for longer than 10 s, accompanied by a parallel reduction of chest and abdominal movements. Combined apnoeic-hypopnoeic index (CAHI) was defined as the number of apnoeic plus hypopnoeic episodes per hour of sleep time. Sleep and apnoeas were scored without knowledge of the treatment regimen. On the evening of the sleep studies, blood was obtained for measurement of serum testosterone by radioimmunoassay, as described previously (Bremner *et al.*, 1981).

On the day following the sleep studies, blood was obtained for determination of haematocrit and arterial blood gases, and awake pulmonary function and ventilatory drive studies were performed. The hypoxic ventilatory response was measured using the isocapnic method of Weil *et al.* (1970) and was expressed as the value A which was determined by the shape parameter of the hyperbolic function derived from plotting minute ventilation ($\dot{V}_E$) vs alveolar P_{O2} (P_{AO2}). The hypercapnoeic ventilatory response was measured using the rebreathing technique of Read (1967) and was expressed as the value S, which was determined by the slope of $\dot{V}_E$ vs alveolar P_{CO2} (P_{ACO2}). Both techniques have been used extensively in our laboratory (Schoene *et al.*, 1981).

Statistical analysis was done by Student's paired t-test. All variances were expressed as standard error of the mean (SEM).

RESULTS

Sleeping ventilatory studies

Two hypogonadal men, Subjects 1 and 2, exhibited marked increases in sleep disordered breathing on testosterone therapy (Fig. 1a). Subject 1 exhibited a substantial number of apnoeic and hypopnoeic episodes while receiving no treatment; he had a combined

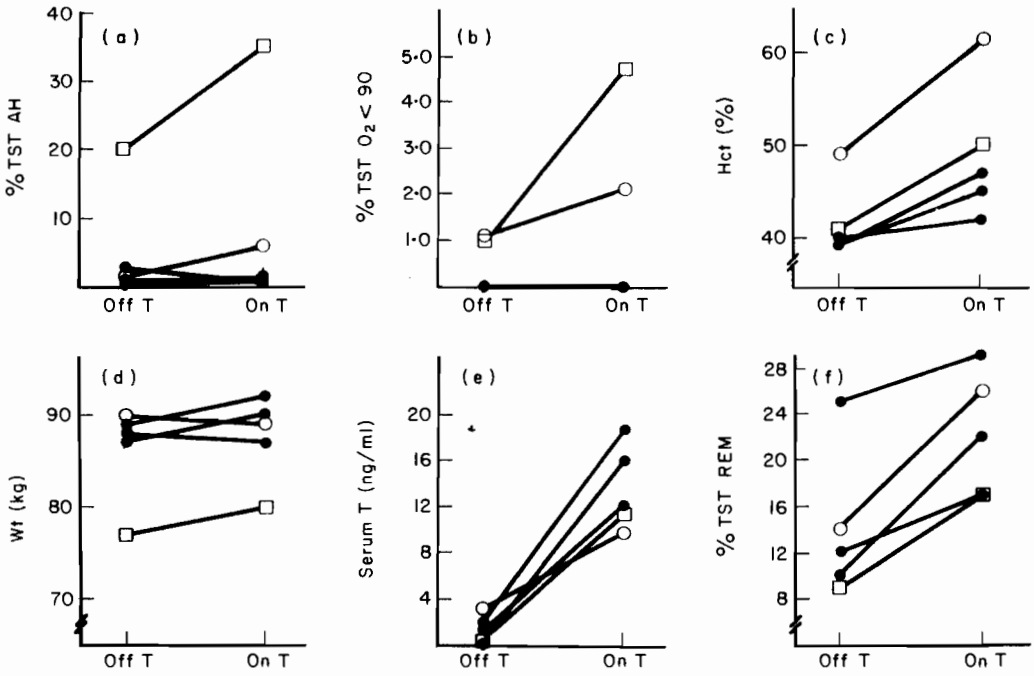

Fig. 1. **a,** The percentage of total sleep time spent in apnoea and hyponoea (%TST AH); **b,** the percentage of total sleep time with oxygen saturation less than 90% (%TST $O_2 < 90$); **c,** haematocrit (Hct); **d,** body weight (Wt); **e,** serum testosterone level (Serum T); and **f,** the percentage of total sleep time spent in REM sleep (%TST REM) for each subject off (left) and on (right) testosterone therapy. (□) Subject 1; (○) Subject 2; (●) Subjects 3–5.

apnoeic-hypopnoeic index (CAHI) of 22 (normal ≤ 5) and 20% of total sleep time (TST) was spent in apnoea and hypopnoea. After 6 weeks of testosterone replacement, CAHI increased to 48 and the amount of TST spent in apnoea and hypopnoea increased to 35%. Subject 2 exhibited normal breathing during sleep off treatment. In this man, CAHI was 3 and apnoeas and hypopnoeas occupied 1·6% of TST off testosterone. With testosterone therapy, CAHI increased to 10 and the amount of TST spent in apnoea and hypopnoea increased to 6·1%. Both of these values were clearly higher than in the remaining hypogonadal men on testosterone. In both Subjects 1 and 2, more than 90% of the apnoeas that occurred were of the obstructive type. Subjects 3, 4, and 5 did not exhibit an abnormal number of apnoeic and hypopnoeic episodes either on or off testosterone treatment.

Subjects 1 and 2 were the only men who developed significant oxygen desaturation during sleep (Fig. 1b). With testosterone therapy, the percentage of TST spent with an oxygen saturation less than 90% increased from 1·0 to 4·7% in Subject 1 and from 1·1 to 2·1% in Subject 2. In addition, Subject 1 developed rapid artrial fibrillation-flutter and Subject 2 developed marked sinus bradycardia in association with episodes of obstructive sleep apnoea and oxygen desaturation during testosterone treatment. The remainder of the subjects maintained oxygen saturation above 90% without cardiac arrhythmias, both on and off testosterone.

Both Subject 1 and 2 were treated on a second occasion with the same dosage regimen

of testosterone (i.e. testosterone oenanthate 200 mg i.m. every 2 weeks for 6 weeks). Subject 1 developed marked difficulty in sleeping, excessive daytime sleepiness and anxiety, and worsening of his previously well-compensated congestive heart failure. As a result, a second formal sleep study on testosterone could not be performed. Subject 2 remained asymptomatic during a second course of testosterone therapy and a repeat sleep study was performed, again two days after his last injection of testosterone oenanthate; this again revealed substantial obstructive apnoea with a CAHI of 24 and 16·4% of TST spent in apnoea and hypopnoea.

Clinical measurements

As described above, Subject 1 developed severe symptoms consistent with obstructive sleep apnoea syndrome during a second course of testosterone therapy. Otherwise, none of the men complained of excessive daytime somnolence, difficulty sleeping, mood depression, oedema, or symptoms of congestive heart failure on or off testosterone.

Haematocrit increased significantly in all subjects from $42 \pm 2\%$ of testosterone to $49 \pm 2\%$ on testosterone ($P < 0{\cdot}01$). Subjects 1 and 2 exhibited the largest incremental rises in haematocrit, as well as the highest absolute values (Fig. 1c). After six weeks of testosterone therapy, haematocrit increased from 41 to 50% in Subject 1 and from 49 to 59% in Subject 2. Of note is that, with more prolonged testosterone treatment, both subjects developed haematocrits above 59%, requiring therapeutic phlebotomy.

There were variable changes in body weight observed with 6 weeks of testosterone treatment in our subjects (Fig. 1d). Subjects 1, 3, and 5 gained 3 kg, while Subjects 2 and 4 lost 1 kg on testosterone replacement. The weight gain in Subject 1 was not associated with oedema, changes in chest radiographs, or other evidence of worsening congestive heart failure.

Serum testosterone levels (determined two days after the last testosterone oenanthate injection) increased significantly in all subjects from a mean of $1{\cdot}3 \pm 0{\cdot}6$ ng/ml to $13{\cdot}6 \pm 1{\cdot}6$ ng/ml during testosterone treatment ($P < 0{\cdot}001$). Subjects 1 and 2 demonstrated serum testosterone levels of 11·7 and 9·8 ng/ml, respectively, two days after their last injection of testosterone oenanthate. These values were lower than those in the remainder of the hypogonadal men on testosterone (Fig. 1e).

Other sleep findings.

All five subjects demonstrated significant changes in rapid eye movement (REM) sleep during testosterone administration (Fig. 1f). The percentage of TST spent in REM sleep increased significantly from a mean of $14 \pm 3\%$ to $22 \pm 2\%$ on testosterone ($P < 0{\cdot}001$). The increases in REM sleep demonstrated by Subjects 1 and 2 were not distinguishable from the other subjects. Furthermore, the majority of apnoeas exhibited by Subjects 1 and 2 occurred during non-REM sleep and most of the increase in obstructive apnoea demonstrated by these men did not occur during REM sleep time. REM latency (time to initial REM episode) also decreased in all subjects, from a mean of 89 ± 12 min to 58 ± 6 min on testosterone ($P < 0{\cdot}05$). TST was not significantly affected by testosterone therapy. Mean TST was $5{\cdot}74 \pm 0{\cdot}52$ h off testosterone and $6{\cdot}03 \pm 0{\cdot}45$ h on testosterone ($P = \text{NS}$).

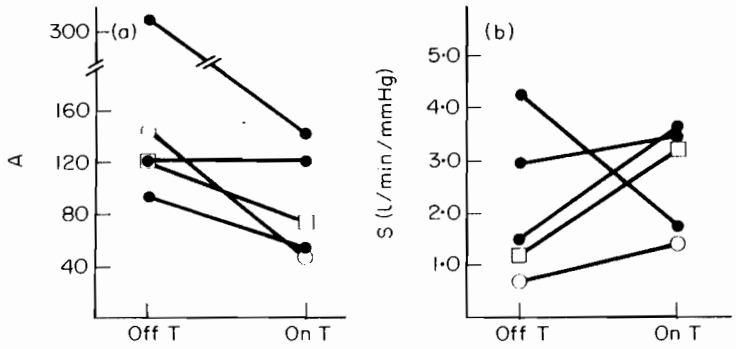

Fig. 2. **a,** Shape (A) of hypoxic ventilatory response and **b,** slope (S) of hypercapnoeic ventilatory response for each subject off (left) and on (right) testosterone therapy. (□) Subject 1; (○) Subject 2; (●) Subject 3–5.

Awake ventilatory studies

Hypoxic ventilatory response (A) decreased significantly in our subjects, from 158 ± 39 off testosterone to 88 ± 19 on testosterone treatment ($P < 0{\cdot}05$) (Fig. 2a). Hypercapnoeic ventilatory response (S) increased on testosterone in four of the five subjects (Fig. 2b), but this change did not achieve statistical significance. Neither the changes in hypoxic nor hypercapnoeic ventilatory drive in Subjects 1 and 2 were distinguished from those in the other subjects.

There were no significant changes in resting awake oxygen consumption ($\dot{V}_{O_2}$) and carbon dioxide production ($\dot{V}_{CO_2}$), forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), PaO_2, $PaCO_2$, or oxygen saturation in our subjects during testosterone therapy. None of the men exhibited resting hypoxemia or oxygen saturation less than 90% during the awake studies either on or off testosterone. The values and changes in these measurements in Subjects 1 and 2 were not distinguishable from those in the other subjects.

DISCUSSION

The ventilatory drive to hypoxia was apparently significantly reduced during testosterone replacement therapy of hypogonadal men. In addition, two of five hypogonadal men developed clear worsening of obstructive sleep apnoea with marked decreases in oxygen saturation, cardiac arrhythmias, and large increases in haematocrit during the administration of exogenous testosterone in replacement dosages. One of these men had significant obstructive apnoea off as well as on testosterone.

All subjects demonstrated an increase in haematocrit on testosterone replacement therapy. The two men who demonstrated worsening obstructive apnoea and oxygen desaturation developed erythrocytosis sufficient to require therapeutic phlebotomy (haematocrits greater than 59%). Increases in hematocrit to within the normal male range usually occur during testosterone therapy of hypogonadal men (Bardin & Paulsen, 1981), related to direct stimulation of the bone marrow as well as increased erythropoietin activity (Shahidi, 1973). Occasionally, marked elevations in haematocrit occur during testosterone replacement in hypogonadal men (Bardin & Paulsen, 1981). Our findings

suggest that development of severe oxygen desaturation in association with obstructive sleep apnoea may contribute to this.

Although not uniformly present, obesity and loud snoring have been associated with the obstructive sleep apnoea syndrome (Guilleminault *et al.*, 1976). All five hypogonadal men in the present study were moderately overweight and all admitted to snoring during sleep. While these factors may have predisposed our subjects to obstructive sleep apnoea, the changes in apnoea observed with testosterone therapy cannot entirely be attributed to changes in body weight. Subject 2, who developed an abnormal number of apnoeic episodes, lost 1 kg on testosterone treatment. Subject 1, who developed the most marked increase in obstructive apnoea, demonstrated a 3 kg weight gain on testosterone, without clinical evidence of worsening heart failure. Such small changes in body weight have not been demonstrated to worsen obstructive sleep apnoea. Two other subjects, who weighed more than Subject 1, also exhibited a 3 kg weight increase on testosterone therapy, without however, an increase in sleep apnoea.

The underlying mechanism responsible for both loud snoring and obstructive apnoea, both of which are more common in men than in women, is abnormal relaxation of the pharyngeal musculature during sleep, as a result of abnormal neuromuscular control and/or anatomic distortion of the upper airway. It is possible that ambient levels of testosterone may affect either of these mechanisms. In this regard, testosterone is known to be a potent neuroendocrine hormone, with multiple effects on central nervous system function, including behaviour and control of gonadotrophin secretion (Bardin & Paulsen, 1981). Furthermore, like other anabolic agents, testosterone is known to increase muscle mass (Wilson & Griffin, 1980; Bardin & Paulsen, 1981). If pharyngeal muscle bulk and/or function were affected by testosterone, this may contribute to the pathophysiology of upper airway occlusion seen in obstructive sleep apnoea.

Studies by other investigators have suggested a relationship between testosterone and sleep disordered breathing. Harman *et al.* (1981) studied breathing disorders during sleep in 14 morbidly obese subjects. None of the seven female subjects had disordered breathing or oxygen desaturation, while six of seven male subjects exhibited abnormal breathing during sleep. The one obese male subject who failed to demonstrate episodes of disordered breathing was clinically hypogonadal and had a low serum testosterone level. Strumpf *et al.* (1978) reported the development of sleep apnoea and the Pickwickian syndrome in an obese hypogonadal man after institution of testosterone replacement therapy. Discontinuation of testosterone, treatment with medroxyprogesterone, and weight reduction resulted in clinical improvement in this man. Recently, Johnson *et al.* (1984) reported the induction of obstructive sleep apnoea on two occasions by exogenous androgen administration in a woman with renal failure and anaemia. Mohamed *et al.* (1983) evaluated 13 women for possible sleep apnoea. Four of these women were found to have obstructive sleep apnoea. Compared to the women without sleep disordered breathing, the women with sleep apnoea had significantly higher levels of the androgens androstenedione, dehydroepiandrosterone sulphate, and free testosterone.

Although not usually successful, progesterone therapy has been reported to improve obstructive apnoea in some patients (Hensley *et al.*, 1980). Furthermore, it is well documented that some men with obstructive sleep apnoea who are treated with high dosages of medroxyprogesterone acetate (MPA) develop symptoms of hypogonadism with diminished libido, impotence, and hot flushes (Hensely *et al.*, 1980). High dosage MPA administration in man results in marked suppression of gonadal function (Southern

et al., 1977; Bardin & Paulsen, 1981). Therefore, it is possible that some of the effectiveness of MPA therapy in sleep apnoea is related to the induction of hypogonadism and diminished serum testosterone levels.

Worsening of apnoeic events and oxygen desaturation have been associated with REM sleep (Guilleminault *et al.*, 1980), which we found to be increased on testosterone replacement therapy. The two subjects who developed increases in obstructive apnoea on testosterone did not exhibit rises in REM sleep that were any greater than those in the other subjects. Furthermore, the majority of apnoeas in these men, both on and off testosterone occurred during non-REM sleep.

Our results suggest that in some men (perhaps with predisposing conditions) replacement dosages of testosterone can worsen or induce obstructive sleep apnoea. These observations, as well as those by other investigators, suggest that androgen levels may contribute to the pathogenesis and prevalence of obstructive sleep apnoea and snoring in men. We recommend that patients receiving testosterone treatment should be monitored for the development of the symptoms and signs of the obstructive sleep apnoea syndrome, such as excessive daytime somnolence, sleep or emotional disturbances, hypertension, oedema, congestive heart failure, or excessive erythrocytosis. These symptoms and signs should prompt consideration of decreasing testosterone treatment, particularly if obstructive sleep apnoea can be demonstrated in formal sleep studies.

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