

# Decreased Pituitary-Gonadal Secretion in Men with Obstructive Sleep Apnea

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Decreased libido is frequently reported in male patients with obstructive sleep apnea (OSA). The decline in morning serum testosterone levels previously reported in these patients was within the normal adult male range and does not explain the frequent association of OSA and sexual dysfunction. We determined serum LH and testosterone levels every 20 min between 2200–0700 h with simultaneous sleep recordings in 10 men with sleep apnea and in 5 normal men free of any breathing disorder in sleep. The mean levels and area under the curve of LH and testosterone were significantly lower in OSA patients compared with controls [LH,  $24.9 \pm 10.2$  IU/liter·h vs.  $43.4 \pm 9.5$  ( $P < 0.005$ ); testosterone,  $67.2 \pm 11.5$  nmol/liter·h vs.  $113.3 \pm 26.8$  ( $P < 0.003$ )]. Four of 10 patients had hypogonadal morning (0700 h) serum testosterone levels. Analysis of co-

variance (ANCOVA) revealed that the 2 groups differed significantly in the amount of LH and testosterone secreted at night independent of age or degree of obesity. After partialing out body mass index, there was a significant negative correlation between the amounts of LH and testosterone secreted at night and the respiratory distress index, but not with degree of hypoxia.

Our findings suggest that OSA in men is associated with dysfunction of the pituitary-gonadal axis. The relation between LH-testosterone profiles and the severity of OSA suggests that sleep fragmentation and, to a lesser extent, hypoxia in addition to the degree of obesity and aging may be responsible for the central suppression of testosterone in these patients. (*J Clin Endocrinol Metab* 87: 3394–3398, 2002)

**O**BSTRUCTIVE SLEEP APNEA (OSA) is a prevalent respiratory disorder affecting 4% of adult males, characterized by repetitive apneic events, typically occurring hundreds of times every night. Apnea-related hypoxia leads to arousal and termination of the obstructive events. Consequently, the repetitive episodes of upper airway obstructions in OSA are associated with severe intermittent hypoxia and sleep fragmentation (1, 2).

Decreased morning testosterone concentrations were found in male patients with OSA and reverted to normal after 3 months of treatment with nasal continuous positive airways pressure. The testosterone decrease was attributed to hypoxia, but because LH secretion was not investigated, the reason for testosterone suppression could not be determined (3, 4). In young normal men there is a sleep-related rise in serum testosterone concentration that is linked with the first rapid eye movement (REM) sleep period (5). Sleep fragmentation disrupted the diurnal testosterone rhythm, resulting in a considerable attenuation of the nocturnal rise (6).

The present study was undertaken to delineate the status of the pituitary-gonadal axis in obstructive sleep apnea. We determined the nocturnal serum LH and testosterone levels, obtained at 20-min intervals, in men with OSA and correlated serum hormone levels with the severity of the syndrome.

Abbreviations: AUC, Area under the curve; BMI, body mass index; CV, coefficient(s) of variation; OSA, obstructive sleep apnea; RDI, respiratory distress index; REM, rapid eye movement.

## Subjects and Methods

### Diagnostic procedure of OSA

Patients evaluated for OSA first completed a comprehensive questionnaire on their sleep and medical history. Diagnostic sleep recordings included electrooculography, electromyography, electroencephalography, respiration, and oxygen saturation. Respiration was recorded using nasal and oral thermistors and a thoracic strain gauge. The oxygen saturation level was determined by a finger pulse oximeter. We determined the lowest and mean nocturnal oxygen saturation as well as the percentage of time spent asleep with oxygen saturation below 90% ( $\text{PaO}_2 < 90\%$ ). Apneas and hypopneas were counted, and the respiratory distress index (RDI) was calculated by dividing their total number by hours of sleep. Apnea was defined as a cessation of airflow through the mouth and nose for more than 10 sec. Hypopnea was defined as a decrease in the amplitude of the respiratory signal of at least 50% for a minimum of 10 sec, followed by either a decrease in oxygen saturation of 4% or signs of physiological arousal. A diagnosis of OSA was based on a combination of characteristic symptoms (loud and disturbing snoring, excessive daytime sleepiness, morning fatigue) and a finding of RDI greater than 10 (1, 7, 8).

### Subjects

Ten men (age,  $46.1 \pm 7.3$  yr) diagnosed as having severe obstructive sleep apnea (RDI,  $52.6 \pm 17.4$ ;  $\text{PaO}_2 < 90\%$ ,  $7.1 \pm 8.8\%$ ) and five healthy controls (age,  $42.0 \pm 13.3$  yr; RDI,  $7.0 \pm 0.8$ ;  $\text{PaO}_2 < 90\%$ ,  $0.1 \pm 0.2\%$ ) participated in the study. All participants underwent whole night conventional sleep recording before the present study. These excluded any breathing disorders during sleep in the controls and established the OSA diagnosis in patients.

The Helsinki Committee of the Afula Medical Center (Afula, Israel) approved the study. All participants gave their informed consent before the start of the study.

### Study protocol

Subjects were admitted to the Sleep Research Center at 1600 h. At 1700 h, an iv catheter was inserted into an antecubital vein and was kept

patient with a slow infusion of 0.9% NaCl. Blood samples (3 ml) were collected every 20 min from 1900–0700 h. From 2200–0700 h, lights were off, and subjects retired to sleep. Conventional sleep recordings were obtained from 2200–0700 h, in single bed, air-conditioned, sound-attenuated rooms.

### Analysis of sleep stages

Electrodes were attached for the following electrophysiological recordings: 2 electroencephalograms (levels C3-A2 and C4-A1), 2 electrooculograms, and 1 electromyogram of the mentalis. Sleep stages were scored in 30 epochs according to conventional criteria (9).

### Hormone measurements

Blood was centrifuged, immediately separated, and stored at  $-20^{\circ}\text{C}$  until assayed. Serum LH and testosterone levels were determined by immunoradiometric technique (Biodata Diagnostics, Rome, Italy). The LH intraassay coefficients of variation (CV) were 2.1% and 3.2% for low (2.2–3.3 IU/liter) and high (27–41 IU/liter) concentrations, respectively. The interassay CV were 3.7% and 0.8%, respectively. The sensitivity of the assay was 0.15 IU/liter. The testosterone intraassay CV were 6.0% and 3.0% for low (2.2–4.0 nmol/liter) and high (29.4–62.0 nmol/liter) concentrations, respectively. The interassay CV were 1.9% and 1.6%, respectively. The sensitivity of the assay was 0.15 nmol/liter.

### Statistical analysis

Mean and integrated [area under the curve (AUC)] serum LH and testosterone concentrations from 1900–0700 h were determined in the two groups. The onset of the testosterone rise was defined as the time of the first occurrence of at least three consecutive samples exceeding the mean levels obtained between 1900 and 2200 h by more than 1 sd. Using the morning (0700 h) testosterone level, we defined hypogonadism as a testosterone level less than 10 nmol/liter (10, 11). Independent two-sample *t* tests were used to compare the mean LH and testosterone levels and the AUC as well as the 0700 h testosterone level between the two groups. Group differences in AUC, sleep stages, number of apneas and hypopneas, RDI, PaO<sub>2</sub> below 90%, body mass index (BMI) were tested by Wilcoxon independent sample test. Spearman rank test was performed, correlating between AUC and RDI, and PaO<sub>2</sub> below 90%. The relationship between LH and testosterone in the two groups was assessed by cross-correlating the hormone levels.

## Results

All subjects completed the experimental paradigm. As expected, patients with OSA had significantly higher RDI and PaO<sub>2</sub> less than 90% compared with controls (Table 1). All patients and controls had REM sleep episodes during the experimental night. The first REM episode was observed at  $0121 \pm 0108$  h in OSA patients *vs.*  $2453 \pm 0480$  h in controls (difference not significant). Likewise, REM latency was not statistically significantly different between the 2 groups ( $0243 \pm 0101$  *vs.*  $0219 \pm 0490$  h). All participants showed a well defined nocturnal testosterone rise. In OSA patients the testosterone onset antedated the appearance of the first REM sleep episode by 53 min compared with 97 min in controls. The control group had significantly higher mean and AUC

**TABLE 1.** Clinical characteristics of the study population (values are given as mean  $\pm$  SD)

Parameter	OSA	Control	<i>P</i>
Age (yr)	46.1 $\pm$ 7.3	42.0 $\pm$ 13.3	NS
BMI (kg/m <sup>2</sup> )	30.6 $\pm$ 4.9	26.3 $\pm$ 2.4	0.1
RDI	52.6 $\pm$ 17.4	7.0 $\pm$ 0.8	0.0003
Apnea	205.6 $\pm$ 166.2	1.4 $\pm$ 0.6	0.003
Hypopnea	121.4 $\pm$ 84.5	31.2 $\pm$ 20.6	0.04
SaO <sub>2</sub> <90%	7.1 $\pm$ 8.8	0.14 $\pm$ 0.26	0.02

values of both LH and testosterone compared with OSA patients (Table 2 and Fig. 1). In 4 of the 10 patients, the morning (0700 h) testosterone levels were below the lower adult male limit of 10.0 nmol/liter (12). After adjustment for BMI, there was a borderline statistically significant difference in the 2 groups in mean LH and testosterone levels [LH-OSA,  $2.2 \pm 0.27$  IU/liter; control,  $3.2 \pm 0.4$  ( $P < 0.076$ ); testosterone-OSA,  $9.4 \pm 1.1$  nmol/liter; control,  $13.7 \pm 1.6$  ( $P < 0.056$ )] and a significant difference in AUC [LH-OSA,  $13.3 \pm 6.3$  IU/liter·h; control,  $41.3 \pm 10.0$  ( $P < 0.008$ ); testosterone-OSA,  $67.2 \pm 11.55$  nmol/liter·h; control,  $113.3 \pm 26.8$  ( $P < 0.003$ )]. Testosterone lagged behind LH by  $73.3 \pm 31.6$  min (median, 80 min) in OSA patients and by  $90.0 \pm 52.9$  min (median, 100.0 min) in controls. There was a statistically significant negative correlation between LH-AUC and RDI ( $r = -0.58$ ;  $P < 0.03$ ) and between testosterone AUC and RDI ( $r = -0.71$ ;  $P < 0.0006$ ), but not with PaO<sub>2</sub> less than 90% (LH AUC:  $r = -0.28$ ;  $P = 0.34$ ; testosterone AUC:  $r = -0.51$ ;  $P = 0.07$ ).

## Discussion

In this study we demonstrated that although sleep apnea patients maintained a normally oriented diurnal rhythm of testosterone, their nocturnal testosterone rise was significantly suppressed compared with that in control men of similar ages. Morning testosterone levels were in the hypogonadal range in 4 of the 10 patients (40%). The amounts of LH and testosterone secreted at night were significantly lower in OSA patients compared with controls independent of age and degree of obesity. We also demonstrated a significant negative correlation between the amounts of LH and testosterone and RDI, but not with the degree of hypoxia.

Several factors may account for the reduced LH and testosterone levels observed in the current study, including advanced age, obesity, hypoxia, and sleep fragmentation. The serum testosterone concentration was shown to decline with increasing age (12–14). Hypogonadal testosterone levels were observed in about 12% of men over 50 yr of age and in 50% of elderly men over 80 yr of age (12). The decrease in testosterone levels with age is considered both central (pituitary) and peripheral (testicular) in origin (11, 15). Others have shown a longitudinal decline in testosterone and an increase in LH and FSH levels in older men (16, 17). In healthy old men, total testosterone, bioavailable testosterone, estrone, total estradiol, and bioavailable estradiol decreased, whereas SHBG increased (17, 18). In our study all control subjects had mean nocturnal and morning (0700 h) testosterone levels within the normal adult male range (13, 19). The reduced testosterone levels in OSA patients were independent of age.

Obesity is common in OSA and is associated with increased severity of sleep apnea, as indicated by the RDI (20). Patients with obesity-hypoventilation syndrome also had sleep apnea (21). Reversible hypogonadism was described in a morbidly obese man whose OSA and low testosterone levels returned to normal after significant weight loss (22). Obesity is associated with reduced SHBG and low testosterone, but normal bioavailable testosterone (23). In massively obese men (BMI,  $>35.1$  kg/m<sup>2</sup>) total testosterone, free

**TABLE 2.** Pituitary-gonadal hormones status in OSA patients and control men

Subject	BMI (kg/m <sup>2</sup> )	LH		Testosterone				
		Mean (IU/liter)	AUC (IU/liter)	Onset (clock h)	Onset (nmol/liter)	0700h level (nmol/liter)	Mean (nmol/liter)	AUC (nmol/liter-h)
1	25.3	1.7	20.1	2200	7.5	8.4	6.5	73.4
2	32.4	1.2	14.1	2300	6.9	8.5	6.6	68.3
3	28.6	0.9	10	2340	7.1	8.4	7.2	67.7
4	29.4	1.8	21.7	0100	11.3	14.5	10.5	77.7
5	29.4	2.8	21.4	0300	15.1	13.8	13.9	68.1
6	27.4	3.5	42.1	0200	15.2	16.9	14.3	62.8
7	38.1	1.8	20.7	0200	8.1	10.9	6.7	37.9
8	40.4	1.4	16.4	0100	12.5	12.6	10.7	73.5
9	27.2	3.1	36.8	2200	9	8	8.2	77.8
10	27.4	2.9	34.4	0040	8.5	10.4	9.7	64.3
Mean ± SD	30.6 ± 4.9	2.1 ± 0.9	24.9 ± 10.2	2428 ± 144	10.0 ± 3.2	11.2 ± 2.9	9.4 ± 2.9	67.2 ± 11.5
1	24.6	4.9	36.7	2140	10.4	11.2	9.9	99.8
2	28.9	2.7	37.5	2400:00	18.7	19.3	16.2	111
3	24.4	3.3	58.9	2320	20.7	21.8	19	160.2
4	29.1	3.1	39.7	2420:00	13	19.6	13.2	99.2
5	24.7	3.1	32.8	2300	10.9	13.5	10.6	96.5
Mean ± SD	26.3 ± 2.4	3.5 ± 0.9	43.4 ± 9.5	2316 ± 102	14.7 ± 4.7	16.9 ± 4.3	13.8 ± 3.8	113.3 ± 26.8
P	0.1	0.02	0.004	NS	0.04	0.03	0.03	0.003

testosterone, and LH significantly decreased to hypogonadal levels. After weight loss, hormone levels significantly increased (24, 25). Lower LH and testosterone values in the current study were independent of obesity, as determined by the analysis of covariance. Moreover, the four patients with hypogonadal morning (0700 h) testosterone levels (>10.0 nmol/liter) had BMI values ( $28.3 \pm 2.6$  kg/m<sup>2</sup>) lower than those in the six patients with normal morning testosterone levels ( $32.0 \pm 5.2$  kg/m<sup>2</sup>). This is in agreement with previous observations suggesting that the abnormalities in testosterone physiology in OSA are distinct from those reported in aging and obesity (3, 4).

The relative importance of hypoxia and sleep fragmentation in the genesis of gonadal dysfunction was examined in the current study and in previous reports (3, 4, 26). In normal young adults, sleep deprivation was associated with suppression of gonadal steroids (27, 28). When OSA patients with severe oxygen desaturation were compared with patients with less severe desaturation, a significant correlation was found between peak testosterone level and total desaturation time, suggesting that hypoxia affected the testosterone circadian rhythm (26). Similar findings were demonstrated in a study comparing testosterone levels with minimum SaO<sub>2</sub>. Neither testosterone nor LH concentrations correlated with apnea index (4). Others have demonstrated that decreased morning testosterone levels, but not LH, were related to the degree of hypoxia, but not to the degree of sleep fragmentation. However, RDI significantly correlated with SHBG levels. In this study only morning testosterone levels were determined in OSA patients (3). Others have found subnormal morning LH levels in 16 men with OSA in whom testosterone levels were normal (29). In the present study after partialing out the influence of BMI, LH AUC and testosterone AUC significantly negatively correlated with RDI, but not with PaO<sub>2</sub> less than 90%. We have no immediate explanation for the discrepancy between our results demonstrating the influence of RDI on testosterone secretion and previous findings emphasizing the degree of hypoxia. It is possible,

however, that both hypoxia and sleep fragmentation influence pituitary-gonadal function in OSA patients. We should note that in a previous study the potential confounding effects of BMI on this relationship were not controlled for as in the present study (4). Our findings on the relationship between RDI and testosterone levels are in agreement with previous results from our laboratory. We showed that in normal young adults, sleep fragmentation was associated with a disruption of the diurnal testosterone rhythm (6). In that study, however, there was a significant relationship between the latency to the first REM period and the nocturnal testosterone rise during continuous sleep, but not during fragmented sleep. No such relationship was found in the current study. Patients with OSA, although having decreased nocturnal LH and testosterone secretion, did not show prolonged REM latencies, and there was no difference between the slopes of the testosterone rise in patients and controls. It should be noted that under the sleep fragmentation paradigm, sleep was repeatedly interrupted for much longer periods than the brief arousal that characterizes the apneic patient.

The reduced amounts of LH and testosterone and their significant association with RDI suggest that the pituitary-gonadal dysfunction is a consequence of OSA, rather than an independent primary disorder of the hypothalamic-pituitary-gonadal axis. Previously, Grunstein *et al.* (3) reported a decline in morning testosterone levels in OSA patients. However, this decline in testosterone levels was within the normal adult male range (12), and does not explain the frequent association of OSA and sexual dysfunction (4, 30). The findings of hypogonadal testosterone levels in 40% of our patients may explain the high frequency of impotence associated with this syndrome (30–32). The interpretability of our results may be limited by the fact that we measured only LH and total testosterone. Several studies have shown that obesity is associated with reduced SHBG and low testosterone, but normal bioavailable testosterone. Non-SHBG-bound testosterone seems to be the best parameter for serum bioactive

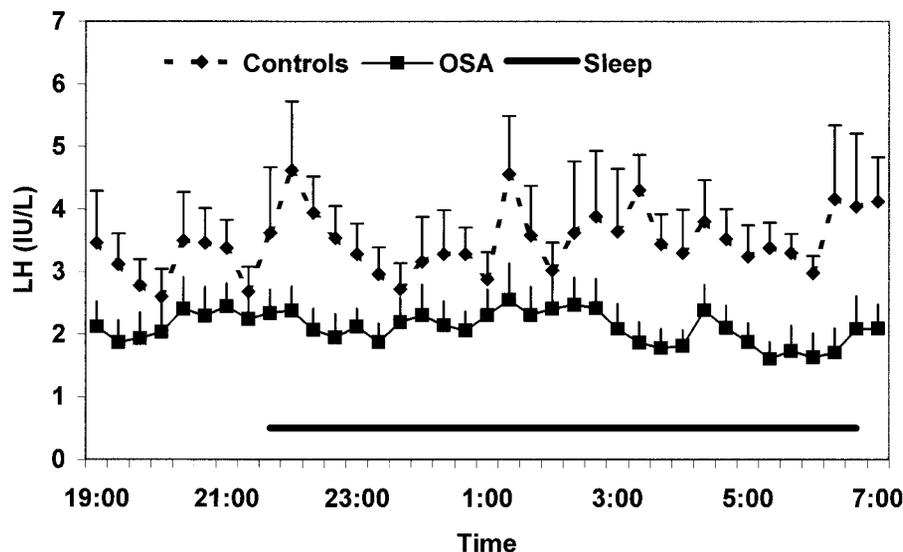
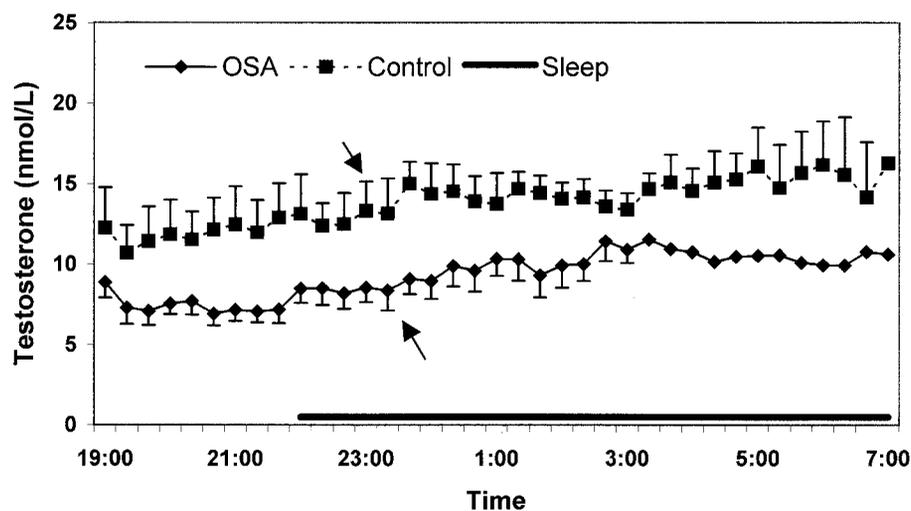


FIG. 1. Effect of sleep apnea on nocturnal LH and testosterone secretion. The first REM sleep episode is indicated by an *arrow*.

#### Mean (SEM) Testosterone Level



hormone (15, 18). In morbid obese men, free testosterone levels were negatively correlated with BMI (24).

Taken together, our findings suggest that men with OSA have decreased nocturnal testosterone levels, possibly due to the combined effect of sleep fragmentation and hypoxia. The role of obesity and aging in decreasing androgen production in these patients cannot be completely excluded at this stage. Further studies are required to clarify whether therapeutic intervention of OSA will reverse this central suppression of the pituitary-gonadal axis.

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