The role of Obstructive Sleep Apnea and CPAP therapy in the functional hypogonadism of male patients with severe obesity

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ABSTRACT

Background: Only a few studies have reported a correlation between severe Obstructive Sleep Apnea Syndrome (OSAS) and hypogonadism in patients with obesity, regardless of body mass index (BMI). However, longitudinal studies exploring the role of continuous positive airways pressure (CPAP) on gonadal function are scanty.

Aim: To investigate in male subjects with severe/complicated obesity the role of OSAS in decreasing testosterone levels and evaluate the effects of CPAP on hormonal status.

Methods: This cross-sectional study consecutively enrolled 204 male inpatients with complicated severe obesity, without known hypogonadism. Polysomnography (or overnight oximetry during CPAP) and blood tests for inflammation, metabolic and hormonal profiles were performed. "Decompensated OSAS" was defined as Apnea/Hypopnea Index (AHI) in newly

diagnosed, or Oxygen Desaturation Index (ODI) in treated patients, above 30 events/hour. A multiple linear regression was implemented to identify the independent factors correlated with total testosterone (TT). Lastly, a longitudinal study of 14 newly diagnosed patients was performed to evaluate the effects of CPAP on TT after 3 months treatment.

Results: 127/204 patients showed low TT (≤10.4 nmol/L). BMI, type 2 diabetes (T2DM), C-reactive Protein (CRP), and decompensated OSAS were independently associated with TT (p-value 0.039, p-value 0.006, p-value 0.003 and p-value 0.014 respectively). After 3 months of CPAP therapy, TT was higher (p-value 0.009) and ODI was associated with such improvement, independently of BMI (p-value 0.04).

Conclusion: decompensated OSAS was found to correlate with low testosterone in males with severe obesity. Moreover, CPAP therapy was shown to improve TT independently of BMI changes.

INTRODUCTION

In 2022, nearly one billion adults were living with obesity worldwide. As reported by the World Health Organization (WHO), obesity is a chronic complex disease defined by excessive fat deposits that can impair health[1]. Indeed, this condition is associated with higher mortality and morbidity rates, particularly from cardiovascular disease, diabetes, and cancer[2]. As regards hormonal alterations, obesity may be both a cause and a consequence of endocrine disorders, and among them low testosterone levels have been well characterized[3,4]. Male hypogonadism has been reported in up to 45% of patients with moderate-severe obesity when considering total testosterone (TT) and/or free testosterone (FT) concentratons[5]. Several mechanisms have been proposed to explain such correlation: while an increase in aromatase activity in adipose tissue and rise in estradiol levels have not been confirmed in recent studies, insulin and leptin resistance and pro-inflammatory adipocytokines may suppress hypothalamic-pituitary-gonadal (HPG) axis, at least in part, via effects

on kisspeptin neurons modulation[6]. Finally, obesity has been associated with Obstructive Sleep Apnea Syndrome (OSAS), a condition characterized by recurrent episodes of partial or complete upper airway collapse during sleep, resulting in reduced (hypopnea) or absent (apnea) airflow, and accompanied by cortical arousal, decrease in blood oxygen saturation, loud snoring and daytime sleepiness[7].

To date, whether OSAS also contributes to the decrease in testosterone blood values in male patients with obesity remains unclear.

Already in 1989, in a cross-sectional study of men undergoing sleep evaluations, Grünstein *et al*. had found that FT, TT, and Sex Hormone Binding Globlulin (SHBG) levels were significantly lower in relation to the severity of sleep apnea; this decrease was independent of the effects of aging and adiposity by covariance analysis. In a longitudinal study, the same authors showed that plasma TT, SHBG, but not FT, significantly increased after 3 months of nasal continuous positive airways pressure (CPAP) treatment[8].

In subsequent studies conducted in small cohorts of patients with obesity, a statistically significant inverse correlation between OSAS and testosterone levels, independent of BMI, was confirmed[9,10], and the severity of hypoxia during sleeping hours was suggested as an additional factor in reducing testosterone levels[11]. A recent work confirmed the association between severity of OSAS and sex hormonal profile in a larger cohort of male patients with obesity, revealing that both Apnoea Hypopnoea Index (AHI) and oxygen desaturation index (ODI) were in significant inverse correlation with total and free testosterone concentrations after adjustment for age and BMI[12].

The mechanisms by which OSAS would lead to reduced testosterone levels are far from being elucidated, but hypoxia and changes in sleep architecture have been reported to impair gonadal axis and gonadotropin secretion[13,14].

The success of CPAP therapy in restoring or improving gonadal function was investigated, but results are inconclusive. A recent meta-analysis including twelve studies did not confirm the positive effect of CPAP therapy on serum testosterone and gonadotropin levels in male patients with OSAS syndrome, suggesting strategies other than CPAP to treat hypogonadism in such patients[15]. Nevertheless, to the best of our knowledge, the effects of CPAP therapy on hormonal outcome have never been evaluated on a population of only patients with obesity.

Therefore, the aim of the present study was to investigate the relationship between obesity, OSAS syndrome and hypogonadism in the largest possible case series of patients with severe/complicated obesity and without ongoing Testosterone Replacement Therapy (TRT), by evaluating the factors associated with hypogonadism. In particular, we investigated (1) the role of the severity/decompensation of OSAS syndrome in the decrease in blood testosterone concentration, adjusting for the other known factors associated with functional hypogonadism in obesity and, (2) the effects of a 3-months-successul CPAP therapy on the gonadal function of a subset of newly diagnosed patients with OSAS.

MATERIALS AND METHODS

Study design

This monocentric cross-sectional study involved 204 male patients with obesity admitted between January 2022 and October 2023 to the San Giuseppe Hospital Centre in Piancavallo (Piemonte, Italy), of Istituto Auxologico Italiano. Male patients with grade II complicated obesity (i.e. BMI ≥35 kg/m^2 and at least one of the following: OSAS, cardiovascular disease, decompensated DMT2, eating disorder, and severe osteoarticular complications) or grade III obesity (i.e. BMI ≥40 kg/m^2) were eligible for inclusion. Patients with already known organic disease affecting the hypothalamic/pituitary region

or, systemic disease, or undergoing treatment with glucocorticoids or other drugs interfering with the gonadal axis were excluded.

In a subset of 14 patients with a new diagnosis of severe OSAS and a good compliance to the ventilation therapy, we also carried out a longitudinal evaluation of the effects of CPAP on testosterone values after 3 months of treatment.

The study was approved by the Institutional Review Board (Istituto Auxologico Italiano, 05C308) and all patients provided written informed consent to allow their de-identified or anonymized data to be used for research purposes.

Procedures

At the time of admission, the following anamnestic data were collected: presence of a previous diagnosis of OSAS and concomitant CPAP or bi-PAP therapy; presence or absence of a previous psychiatric diagnosis of Binge Eating Disorder (BED), according to DSM-V diagnostic criteria, and a previous diagnosis of T2DM. BMI was calculated as the ratio of weight to height squared and the waist circumference (WC) was measured using a tailor's tape measure (i.e. flexible but not stretchable), or similar tape measures, on patient placed in orthostatism and with the abdomen completely uncovered by clothing.

From the blood tests performed on admission, the following were collected: inflammation indices (ESR and CRP), glycaemic balance (basal glucose, insuline and glycated haemoglobin [HbA1c]), lipid profile (total cholesterol, HDL and triglycerides), hormone profile (TT, Luteinizing Hormone [LH] and Follicle-stimulating hormone [FSH]). All samples for TT and gonadotropin determination were collected between 8 and 10 a.m. During admission, if OSAS had never been diagnosed, patients underwent polysomnography, and the AHI values were collected. All polysomnographic monitoring was performed with the same equipment, namely a SOMNOscreen (SOMNOmedics, Italy).

On the other hand, if OSAS had already been diagnosed, overnight pulse oximetry was performed under CPAP ventilatory support, and ODI values were collected. Each overnight pulse oximetry record was performed with the PULSOX pulse oximeter (Konica Minolta, Inc.).

In a subset of 14 newly diagnosed patients with OSAS who started CPAP therapy, TT and BMI were measured after 3 months of successful CPAP therapy (ODI <15) to assess the independent effect of the treatment on the gonadal function.

Assays

Testosterone was evaluated using the Elecsys Testosterone II assay (Calibrator reference: 05200067190) (Roche Cat#07027915190, RRID: AB_3101983) manufactured by Roche Diagnostics®, and has a lower limit of detection of 0.087 nmol/L and a functional sensitivity of 0.4 nmol/L, with a measurement range of 0.087-52.0 nmol/L. The assay method has a cross-reactivity of 2.5% for Androstenedione; 0.01% for Cortisol, DHEA, DHEA-S; 0.001% for Cortisone, Dexamethasone, Progesterone; 0.5% for Danazol; 0.16% for Estradiol; 0.004% for Estrone; 2.4% for Etisterone; 0. 9% for Norgestrel; 2.46% for Testosterone propionate; 0.86% for Dihydrotestosterone; 18% for 11-b-Hydroxytestosterone; 3.22% for 11-Ketotestosterone; 6% for 10-Norethisterone; 0.002% for Prednisone. This method is standardised by liquid chromatography/mass spectrometry. LH and FSH concentrations were measured by Elecsys LH (Roche Cat#07027575190, RRID: AB_2920601) and Elecsys FSH (Roche Cat#09745840, RRID: AB_3678555) from Roche Diagnostics®. The LH and FSH assays had a minimum detection limit of 0.1 IU/L and a functional sensitivity of 0.2 IU/L, with a measurement range of 0.1-200 IU/L. In the FSH assay method there is a cross-reactivity <0.1% for LH, TSH, hCG, hGH, hPL. The LH assay method has a cross-reactivity <0.1% for FSH, TSH, hCG, hGH, hPL. Elecsys insulin (Roche Cat#07027559, RRID: AB_2909455) was used to measure insulin, and CRP levels were assessed by ELISA kits (Hytest Cat# 4C28cc-CRP135cc, RRID: AB_2889099).

Statistical analysis

Results are presented as count (%) or mean ± standard deviation depending on the data type and distribution. Groups were compared with nonparametric tests (Mann-Whitney U test and Kruskal-Wallis test). A multivariate linear regression was also performed to assess the relationship between the progressive reduction of blood values of testosterone and the following independent variables: BMI, severe/decompensated OSAS, previous diagnosis of eating disorder, age, blood values of CRP and diagnosis of T2DM. All p values below 0.05 were considered significant. To evaluate the effect of CPAP therapy on the hormone profile, testosterone values pre- and post- ventilatory treatment were analyzed with Wilcoxon signed-rank test and a multiple linear regression was finally performed to correlate serum testosterone levels with ODI adjusting for BMI. All data were analyzed using IBM® SPSS® Statistics 29.0.

RESULTS

The characteristics of the population are shown in **Table 1**. The population was aged between 18.1 and 87.8 years, with BMI between 35.39 kg/m^2 and 126.4 kg/m^2, and a waist circumference between 112 cm and 215 cm. Among the enrolled patients, 187 patients had either previously diagnosed or newly diagnosed OSAS. No patient had Central Sleep Apnea. 83 new diagnoses of OSAS were defined by AHI values at polysomnography performed at admission ≥ 15 events/hour. Severe/decompensated OSAS (s/dOSAS), defined as AHI (or ODI) above 30 events/hour, was reported in 112 patients undergoing either polysomnography or overnight pulse oximetry during admission. Overall, the study population showed indices of inflammation compatible with low grade inflammation. 127 patients met the criteria for low testosterone levels (TT ≤10.4 nmol/L), according to the diagnostic criterion adopted in previous studies and world widely accepted for biochemical assessment of hypogonadism in men[16–18]). Among them, 45 subjects (35.4%) showed a marked reduction of gonadal function (TT <6.0 nmol/L). 76.6% of patients with hypoandrogenemia and

concomitant evaluation of gonadotropins had a hypogonadotropic form (LH <9.4 mU/L). In a subgroup of 51 patients in whom SHBG measurement was available, the mean concentration of this protein in patients with severe/decompensated OSAS was comparable to that in the rest of the population (31.6 nmol/L ± 13.21 vs 32.23 nmol/L ± 11.94, p-value = 0.79). Patients were divided according to AHI or ODI values into two groups: absent or mild-moderate/compensated OSAS (AHI/ODI <30/hour) and severe/decompensated OSAS (s/dOSAS, AHI/ODI ≥30/hour). Patients with s/dOSAS were younger, had higher BMI, WC and CRP levels, but a lower prevalence of T2DM when compared with absent/mild/compensated OSAS patients (**Table 1**). Also TT levels were significantly lower in s/dOSAS (p-value = 0.002) (**Figure 1**). No difference in TT was found when we classified patients simply according to the presence or absence of a diagnosis of OSAS (p-value = 0.951). We repeated the comparative statistical analysis for testosterone levels after breaking the population down into three groups (no OSAS, mild OSAS, and severe OSAS), using the Kruskal-Wallis test. The difference in total testosterone among the groups remains statistically significant (p-value = 0.003).

In multiple linear regression analysis, after adjustment for age, BMI, T2DM, BED and CRP values, s/dOSAS was still significantly associated with TT levels (p-values 0.014). Also BMI, T2DM and CRP blood concentrations were found to be in significant correlation with blood TT concentrations (p-value = 0.039, p-value = 0.006 and p-value = 0.003, respectively). The results of the abovementioned model are shown in **Table 2**. These associations were also confirmed when excluding from the analysis the forms of hypergonadotropic hypogonadism (LH ≥ 9.4 mU/L), which accounted for the minority of patients with hypogandrogenemia.

After 3 months of CPAP therapy, testosterone values were found to be significantly improved (**Figure 2**, p-value = 0.009), with an average increase of 3.75 nmol/L (±4.11). Moreover, there was a significant negative correlation between TT and ODI (p- value = 0.04) levels, independently of BMI, in multiple

linear regression (as shown in **Figure 3**). Every patient had an ODI on CPAP therapy < 15 events/hour, so CPAP therapy was considered successful.

Eight of the fourteen patients analyzed longitudinally had baseline gonadotropin assessments. The mean LH and FSH values were 8.02 (±2.14) mU/L and 7.32 (± 6.32) mU/L, respectively, and only one patient out of eight had a condition of hypergonadotropic hypogonadism (LH = 12.9 mU/L).

DISCUSSION

To the best of our knowledge, this is the largest study conducted on male patients with severe obesity with the aim of investigating the contribution of OSAS to functional hypogonadism. It appears, in fact, that hypogonadism in patients with obesity is multifactorial. It is well known that BMI and WC correlate with the severity of hypogonadism[19], and alterations in glucose metabolism, that often accompany severe obesity as part of the metabolic syndrome (hence the term "diabesity"), are also associated with decreased testosterone levels[20]. Consistently, T2DM independently correlates with TT also in our study, suggesting an additional mechanism in the reduction of testosterone production.

In the dysmetabolic patient, it was initially hypothesized that a suppressive effect on the HPG axis may be exerted by higher levels of circulating estrogens due to increased aromatase activity in adipose tissue. Recent evidences however, pointed to dysregulated insulin and leptin signaling, via effects on KNDy (kisspeptin/neurokinin B/dynorphin) neurons in the arcuate nucleus of the hypothalamus[6] , and low-grade inflammation, as the origin of HPG axis dysfunction resulting in decreased gonadotropin secretion[21]. Indeed, some authors described that high fat diet determined a significant microglial activation, expression and immunopositivity of IL-6, and reduced immunopositivity for KISS1 receptor in the hypothalamus of rabbits[22].

Our results are consistent with these data, showing that hypoandrogenemia had a high prevalence in patients with obesity, and T2DM and CRP blood concentrations were independently associated with lower levels of TT in this population. However, as typical of functional forms, most had slightly reduced testosterone levels, and only a smaller but still significant percentage of subjects had severe hypogonadism[23,24].

Also sleep breathing disorders are directly caused by obesity: increased fat mass, particularly in the neck, and reduced chest wall lung compliance lead to repeated episodes of apnea during sleep. The resulting recurrent hypoxia and associated activation of the sympathetic nervous system and other stress responses can ultimately contribute to higher rates of hypertension, metabolic syndrome, and type 2 diabetes, making OSAS an important condition that further complicates organ dysfunction in such patients and requires appropriate management in rehabilitation treatments of obesity[25].

Whether OSAS also contributes to gonadal dysfunction, on the other hand, is still controversial: several studies have investigated a possible association between this syndrome and male hypogonadism with contradictory results[8–10,12,13,15,26,27]; however, only a few of these studies have focused on a homogenous cohort of only patients with severe/complicated obesity and have often been conducted on limited samples[9,10,12]. Nevertheless, these three studies had highlighted the significant association of apnea severity with decrease in blood testosterone concentration, independently of BMI and, in the study of Tančić-Gajić, M. *et al*., also of Metabolic Syndrome. Some authors have tried to explain the possible mechanisms underlying this association: sleep fragmentation in subjects who did not show REM sleep disrupted the testosterone rhythm with a considerable attenuation of its nocturnal rise[28]. In addition, hypoxia may be another responsible for the central suppression of HPG in subjects with OSAS syndrome[29] or other lung diseases[30]

Thus, it could be hypothesized that resolution of sleep fragmentation and nocturnal hypoxia by CPAP therapy could lead to an improvement in testosterone levels. However, most studies did not confirm

this benefit in patients with OSAS, as evidenced by two meta-analyses[15,31]. However, among the included papers, the majority was represented by observational studies with low number of participants, and short duration of the follow-up; moreover, only a few studies reported an adequate CPAP use. In our longitudinal study, on the other hand, we included only patients who had a good compliance to the therapy, finding not only an improvement of testosterone levels after treatment, but also that ODI (measured by overnight pulse oximetry under CPAP therapy) negatively correlated with TT values, even after adjustment for BMI. This finding is particularly relevant since adequate CPAP therapy appears to improve testosterone levels in patients with severe OSAS, with potential benefits on several grounds, including sexual and bone health.

We acknowledge some limitations: a complete assessment of sex hormone profiles was only possible in a subgroup of our population, since SHBG (and calculated free testosterone), gonadotropins, and estradiol measurements were only available in some of the patients, and hypogonadism-related manifestations were not systematically collected. Moreover, the longitudinal study was conducted only in a subset of participants.

Nevertheless, the greatest strength of the study lies in the largest population of patients with obesity ever studied for the correlation between functional hypogonadism and OSASS.

Furthermore, given the monocentric nature of the study, the entire population was studied using uniform procedures and tests. As regards the lack of calculated free testosterone, we found comparable levels of SHBG among patients with severe/decompensated OSAS and absent/mild OSAS: the calculated free testosterone is therefore not expected to show a different trend from that of the total testosterone between the two groups. Lastly, to our knowledge, this is the first study to evaluate the effect of CPAP therapy on testosterone values in a cohort of only patients with obesity.

In conclusion, the presence of untreated severe OSAS or OSAS treated with poor disease control contributes to the decrease in testosterone levels in patients with severe obesity. This effect is

synergic but independent of other factors impairing hypothalamic-pituitary-gonadal function in obesity, such as low-grade inflammation, BMI and diabetes mellitus. In these patients, proper use of CPAP verified by overnight pulse oximetry has a positive effect on serum testosterone concentrations. In patients with obesity-related functional hypogonadism, a successful treatment of OSAS could help, along with weight loss and management of metabolic alterations, to restore proper gonadal function.

DATA AVAILABILITY

Original data generated and analyzed during this study are included in this published article or in the data repositories listed in References.

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1 **Tables**

2 **Table 1** General characteristics of the study population.

	Total cohort (204)	**Absent or m/cOSAS (92)**	**s/dOSAS (112)**	**p value**
Age	56.71 ± 13.58	57.13 ± 13.34	55.90 ± 12.36	0.017
Antropometry and Clinical History				
BMI	47.45 ± 10.97	45.05 ± 6.32	49.56 ± 11.86	<0.001
WC	141.87 ± 15.47	137.86 ± 12.95	145.32 ± 16.60	0.001
T2DM	83/204 (40.68%)	39 (43.39%)	44 (39.28%)	0.017
BED	45/204 (22.05%)	21 (22.82%)	24 (21.42%)	0.92
OSAS	187/204 (91.66%)	-	-	-
s/dOSAS	112/204 (54.90%)	-	-	-
Biochemistry				
CRP (mg/dl)	0.87 ± 0.49	0.77 ± 2.47	0.97 ± 2.73	0.015
ESR (mm/h)	38.20 ± 23.81	40.35 ± 23.23	44.28 ± 25.20	0,063
FPG (mg/dl)	116.96 ± 38.51	111.72 ± 31.18	120.04 ± 40.51	0,216
HbA1c (mmol/mol)	47.51 ± 17.77	45.64 ± 15.93	48.48 ± 18.51	0,245
Insulin (µUI/ml)	21.58 ± 12.12	20.9 ± 12.78	22.28 ± 11.78	0,442
Total cholesterol (mg/dl)	170.29 ± 42.64	159.09 ± 38.34	187.02 ± 42.32	0.001
HDL (mg/dl)	40.16 ± 16.33	39.72 ± 9.47	40.82 ± 11.35	0.382

Triglycerides (mg/dl)	166.31 ± 76.01	99.41 ± 75.57	113.92 ± 72.65	0.044
Total Testosterone (nmol/L)	9.77 ± 4.85	9.78 ± 5.12	8.38 ± 4.41	0.002
LH (mU/L)	7.58 ± 4.76	7.44 ± 3.83	7.66 ± 5.26	0.69
FSH (mU/L)	7.3 ± 6.01	7.92 ± 6.72	6.2 ± 4.52	0.34

m/cOSAS, mild-moderate/compensated Obstructive Sleep Apnea; s/dOSAS, severe/decompensated Obstructive Sleep Apnea; BMI, Body Mass Index; WC, Waist Circumference; T2DM, Type 2 Diabetes Mellitus; BED, Binge Eating Disorder; OSAS, Obstructive Sleep Apnea; CRP, C-reactive Protein; ESR, Erythrocyte Sedimentation Rate; FPG, Fasting Plasma Glucose; HbA1c, Hemoglobin A1c; HDL, High Density Lipoprotein; LH, Luteinizing Hormone; FSH, Follicle-Stimulating Hormone. Data are expressed as mean SD ± or number (percentage). Mann-Whitney U test was implemented to compare groups.

Table 2 Factors associated with blood total testosterone concentrations.

	TT (Total cohort)	
	beta	P value
Age	0.009	0.906
T2DM	-0.185	**0.006**
BED	-0.129	0.070
BMI	-0.150	**0.039**
CRP	-0.207	**0.003**
s/dOSAS	-0.165	**0.014**

T2DM, Type 2 Diabetes Mellitus; BED, Binge Eating Disorder; BMI, Body Mass Index; s/dOSAS, CRP, C reactive Protein; severe/decompensated Obstructive Sleep Apnea. The statistical analysis was performed using multiple linear regression.

Figures

Figure 1 Comparison of testosterone levels between absent or mild-moderate/compensated OSAS and severe/decompensated OSAS.

T, testosterone; s/dOSA, severe/decompensated Obstructive Sleep Apnea; a/m/cOSA, absent/mild-moderate/compensated Obstructive Sleep Apnea.

Figure 2 Testosterone values before and after 3 months of CPAP therapy.

T, testosterone. Before and After CPAP therapy.

Figure 3 Correlations between total testosterone with oxygen desaturation index in patients undergoing successful CPAP therapy.

T, testosterone; ODI, Oxygen Desaturation Index. Yellow spots: before successful CPAP therapy, blue spots: after successful CPAP therapy.

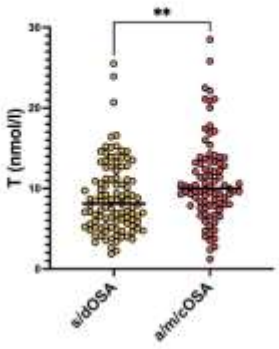

Figure 1
210x297 mm (x DPI)

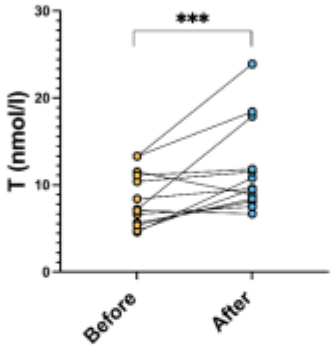

Figure 2
210x297 mm (x DPI)

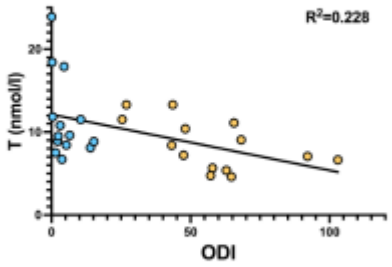

Figure 3
210x297 mm (x DPI)