

Gender Differences in Comorbidities and Sleep Patterns of Obese Patients with Obstructive Sleep Apnea

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Abstract

Objective: The aim of the study was to compare the comorbidities and sleep patterns most commonly associated with each gender in obstructive sleep apnea (OSA). **Methods:** This was a cross-sectional study of obese individuals with OSA. The polysomnographies were carried out in a sleep laboratory environment, using a 15-channel polysomnography setup. Airflow was measured using a nasal pressure cannula/thermistor combination. A standard handbook was used for interpretation of PSG findings. **Results:** A total of 284 subjects were included in the study, (147 females). The mean age, body mass index and neck circumference were similar between females and males ($p = 0.9579$, $p < 0.0001$, and $p < 0.0001$, respectively). On polysomnography, females exhibited longer latency to REM sleep (146.50 ± 85.93 vs. 122.3 ± 68.28 , $p = 0.0210$) and a higher percentage of delta sleep (10.09 ± 7.48 vs. 7.55 ± 6.57 , $p = 0.0037$); males had more frequent microarousals (38.37 ± 27.44 vs. 28.07 ± 21.23 , $p = 0.0017$) and a higher AHI score (30.56 ± 27.52 vs. 17.31 ± 21.23 , $p < 0.0001$). The comorbidities most commonly associated with female gender were diabetes (29% vs. 9.49%, $p = 0.0132$), hypothyroidism (20% vs. 2.19%, $p < 0.0001$), and depression (81.63% vs. 51.22%, $p < 0.0001$). Male gender was associated with myocardial infarction (6.57% vs. 1.38%, $p = 0.0245$) and alcohol intake (33.88% vs. 11.34%, $p < 0.0001$). Obese males with OSA have a larger neck circumference and higher AHI and arousal indices than females. **Conclusions:** There are gender differences both in the sleep patterns and in the comorbidities of patients with OSA. Men had a larger neck circumference, higher apnea and sleep fragmentation scores, were more likely to consume alcohol, and were more likely to have a history of myocardial infarction than women.

Keywords

Obstructive Sleep Apnea, Obesity, Gender, Comorbidity

1. Introduction

OSA (obstructive sleep apnea), the most common respiratory disorder of sleep, is caused by the loss of upper airway dilating muscle activity during sleep superimposed on a narrow upper airway. This results in recurrent nocturnal asphyxia. Termination of these events usually requires arousal from sleep and results in sleep fragmentation and hypoxemia, which leads to poor quality sleep, excessive daytime sleepiness, reduced quality of life and numerous other serious health consequences [1].

OSA and obesity are two major public health issues, both of which have become increasingly common over the past few decades [2] and obesity is considered the significant predictor of OSA [3]. Whereas the overall, population-wide prevalence of OSA is estimated at 4% in men and 2% in women [4], the prevalence of this syndrome in obese persons ranges between 42% and 48% in men and 8% to 38% in women [5]. Patients with these conditions, whether in isolation or occurring concomitantly, are at higher risk of cardiovascular, cerebrovascular, and behavioral comorbidities, and this scenario is associated with a major financial impact on health systems. The treatment costs of obese patients tend to be 36% higher than those of non-obese individuals [2]. Taking into account medical costs, accidents, and occupational losses, the annual economic burden of OSA has been estimated at several billion dollars [6].

Changes in sleep architecture are also quite common in these patients. Studies published in 2009 by Rao *et al.* [7] and Theorell-Haglow *et al.* [8], assessing men and women respectively, found an association between obesity and decreased slow-wave sleep. Resta *et al.* reported severely fragmented sleep and predominance of apnea during the REM (Rapid Eye Movement) stage in obese women as compared with obese men [9]. However, only 45 subjects were assessed. Findings suggest that increased body fat contributes to the pathogenesis of OSA more in males than in females and that obesity plays a more significant role in contributing to OSA in male patients [10].

The present study sought to determine the comorbidities most commonly associated with OSA in each gender and conduct a polysomnography (PSG)-based comparison of sleep architecture in a sample of 284 obese men and women.

2. Materials and Methods

2.1. Study Design

This was a cross-sectional chart review study of obese individuals who underwent overnight PSG at the sleep disorders laboratory of Brasília University Hospital between 2007 and 2010.

The study was analyzed and approved by the local research ethics committee (institutional review board-equivalent).

2.2. Study Population

All patients provided written informed consent for participation. The study sample comprised 284 participants, 137 males (48.2%) and 147 females (51.8%), with a body mass index (BMI) ≥ 30 kg/m². Patients with narcolepsy or idiopathic hypersomnia, neuromuscular disorders, psychiatric disorders, or severe heart or lung disease were excluded from the sample, as were pregnant women and participants whose PSGs were affected by technical difficulties.

The following comorbidities were selected for assessment and comparison: arterial hypertension, cardiac arrhythmias, acute myocardial infarction, congestive heart failure, angina diabetes mellitus, hypothyroidism, depression, asthma, and chronic obstructive pulmonary disease (COPD). The prevalence of two relevant social habits—alcohol intake, defined as regular intake of alcoholic beverages at least once weekly, and smoking, defined as self-reported daily use of tobacco—was also assessed, and Epworth Sleepiness Scale (ESS) scores were calculated for all participants.

2.3. Polysomnography Protocol

All studies were carried out under the supervision of trained polysomnography technologists, in a sleep laboratory environment, using a 15-channel polysomnography setup. Airflow was measured using a nasal pressure cannula/thermistor combination. Hypopnea was defined as a 30% reduction in respiratory flow with a concomi-

tant > 4% reduction in oxygen saturation (SaO₂). A standard handbook was used for analysis and interpretation of PSG findings.

The following polysomnography parameters were selected for analysis and comparison: sleep latency (LAT), latency to REM sleep (LAT_{REM}), lowest recorded SaO₂ (SAT_{MIN}), percentage of total sleep time (TST) spent below SaO₂ < 90% (T90), percentage of TST spent in delta sleep (%Delta), percentage of TST spent in REM sleep (%REM), apnea-hypopnea index (AHI), and number of microarousals per hour of sleep (MICRO).

2.4. Statistical Analysis

Continuous variables were expressed as means and standard deviations, and categorical variables, as relative frequencies (percentages). The Student *t*-test was used for between-gender comparison of normally distributed continuous variables (as determined by the Kolmogorov-Smirnov test). The Mann-Whitney U was used in case of non-normal distribution. The chi-square or Fisher's exact tests were used as appropriate for between-gender comparison of categorical variables. The significance level was set at $p < 0.05$. All statistical analyses were performed in the SAS 9.2 for Windows software package.

3. Results

The variables of interest were classified as anthropometric and social (**Table 1**), polysomnographic (**Table 2**), or comorbidity-related (**Table 3**).

Table 1. Sample profile according to gender.

Variable	Overall	Males	Females	<i>p</i>
Age (years)	45.65 ± 13.98	45.69 ± 14.48	45.60 ± 13.56	0.9579
BMI (kg/m ²)	37.80 ± 7.22	35.56 ± 5.37	39.89 ± 8.07	<0.0001
NC (cm)	41.81 ± 4.22	44.51 ± 3.10	39.26 ± 3.50	<0.0001
ESS score (points)	10.44 ± 4.90	10.13 ± 4.64	10.74 ± 5.15	0.3799
Alcohol intake (%)	23.85	33.88	11.34	0.0001
Smoking (%)	9.13	9.84	8.25	0.6852

Variables expressed as mean ± standard deviation unless otherwise noted. BMI, body mass index; ESS, Epworth Sleepiness Scale; NC, neck circumference.

Table 2. Polysomnography parameters according to gender.

Variable	Overall	Males	Females	<i>p</i>
Lat (min)	18.68 ± 26.00	18.82 ± 29.69	18.55 ± 22.14	0.5934
Lat _{REM} (min)	134.58 ± 78.53	122.30 ± 68.28	146.50 ± 85.93	0.0210
%Delta (%)	8.87 ± 7.15	7.55 ± 6.57	10.09 ± 7.48	0.0037
%REM (%)	17.54 ± 8.12	18.27 ± 7.93	16.86 ± 8.28	0.1447
Sat _{MIN} (%)	76.42 ± 12.36	76.35 ± 11.60	76.48 ± 13.09	0.5030
T90 (%)	23.08 ± 31.72	18.81 ± 26.67	27.12 ± 35.47	0.8711
AHI (n/h)	23.70 ± 24.19	30.56 ± 27.52	17.31 ± 18.54	<0.0001
MICRO (n/h)	33.04 ± 24.91	38.37 ± 27.44	28.07 ± 21.23	0.0017

Lat, sleep latency; Lat_{REM}, latency to REM sleep; %Delta, percentage of sleep time spent in delta sleep; %REM, percentage of sleep time spent in REM sleep; Sat_{MIN}, lowest recorded oxygen saturation; T90, percentage of recorded sleep time spent with oxygen saturation < 90%; IAH, apnea-hypopnea index; MICRO, number of microarousals per hour of sleep.

Table 3. Prevalence of comorbidities according to gender.

Variable	Overall	Males	Females	<i>p</i>
Hypertension (%)	58.30	57.66	58.90	0.8326
Acute myocardial infarction (%)	3.90	6.57	1.38	0.0245
Cardiac arrhythmia (%)	2.50	1.46	3.45	0.4486
Congestive heart failure (%)	0.70	0.00	1.38	0.4986
Angina (%)	0.00	0.00	0.00	-
Stroke (%)	0.00	0.00	0.00	-
Diabetes mellitus (%)	14.80	9.49	29.00	0.0132
Hypothyroidism (%)	11.30	2.19	20.00	<0.0001
Depression (%)	50.40	51.22	81.63	<0.0001
Asthma (%)	20.10	21.90	18.62	0.4934
Chronic obstructive pulmonary disease (%)	1.10	0.73	1.38	1.0000

3.1. Anthropometric and Social Variables

Mean BMI in the overall sample was 37.80 ± 7.22 kg/m² (35.56 ± 5.37 kg/m² in men vs. 39.89 ± 8.07 kg/m² in women, $p < 0.0001$). There was a significant between-gender difference in neck circumference. Mean circumference was 41.81 ± 4.22 cm overall and 44.51 ± 3.10 cm in men versus 39.26 ± 3.50 cm in women ($p < 0.0001$). Alcoholism was also significantly more prevalent among male participants (33.88%) versus female subjects (11.34%) ($p = 0.0001$). The overall prevalence was 23.85%.

There were no significant between-gender differences in age, smoking prevalence, or ESS scores. A detailed list of these variables, including means, standard deviations, and *p*-values of between-gender comparison, is shown in **Table 1**.

3.2. Polysomnography Parameters

Overall, the mean LAT_{REM} was 134.58 ± 78.53 minutes (122.30 ± 68.28 minutes in men vs. 146.50 ± 85.93 minutes in women, $p = 0.0210$). Mean %Delta was $8.87\% \pm 7.15\%$ ($7.55\% \pm 6.57\%$ in men vs. $10.09\% \pm 7.48\%$ in women, $p = 0.0037$). The mean AHI score was 23.70 ± 24.19 events per hour (30.56 ± 27.52 in men vs. 17.31 ± 18.54 in women, $p = 0.0001$). Finally, the mean number of microarousals was 33.04 ± 24.91 per hour in the sample as a whole (38.37 ± 27.44 in men vs. 28.07 ± 21.23 in women, $p = 0.0017$).

No other polysomnography parameters were found to have significant gender differences. Means, standard deviations, and *p*-values of between-gender comparisons are shown in **Table 2**.

3.3. Comorbidities

Overall, 3.9% of participants had a history of myocardial infarction (6.57% of males and 1.38% of females; significant association with male gender, $p = 0.0245$). Diabetes mellitus was reported by 14.8% of participants—9.49% of men and 29% of women—and was significantly associated with female gender ($p = 0.0132$). Hypothyroidism was reported by 11.3% of participants (2.19% of men and 20.00% of women; $p < 0.0001$). Depression was reported by 50.40% of participants (51.22% of men and 81.63% of women) and was also significantly associated with female gender ($p < 0.0001$).

No other comorbidities were significantly associated with gender. Means and *p*-values of between-gender comparison of these conditions are shown in **Table 3**.

4. Discussion

This study assessed a clinical population of obese adults with a similar number of participants and age distribution across both genders.

The association between OSA and obesity has been conclusively established for decades [11]. However, controversy remains as to the possibility that gender differences in the features of obesity may have an impact on the incidence, prevalence, predominance and severity of OSA [10].

In men, adipose tissue tends to build up predominantly in the abdomen and neck area, versus the hips, thighs, and gluteal area in women [12]. Fat buildup in the neck region is considered a relevant predictor of OSA severity; in fact, neck circumference measurement has become a routine part of the assessment of patients with sleep-disordered breathing. A study by Dancey *et al.* suggests that larger neck circumference, which occurs predominantly in men, accounts for only 20% of AHI variability [13]. Simpson *et al.* suggest that, contrary to current belief, OSA severity is associated with abdominal obesity in men and upper airway obesity in women [12]. In our sample, however, women with OSA had higher BMI than men (39.89 ± 8.07 vs. 35.56 ± 5.37 kg/m², $p < 0.0001$), whereas men had larger neck circumference (44.51 ± 3.10 vs. 39.26 ± 3.50 cm, $p < 0.0001$) and more severe disease as measured by the AHI (30.56 ± 27.52 vs. 17.31 ± 18.54 , $p < 0.0001$). This is consistent with prior reports [14] [15].

Gender differences in the daytime sleepiness reported by OSA patients are also a point of contention. In 1993, Young *et al.* found that sleepiness was more common among women with OSA than in men with the condition [16]. However, their assessment was not based on the ESS, which has become the standard method for assessment used in most of the literature. In 1999, Gottlieb *et al.* analyzed the Sleep Heart Health Study sample and found that, despite significantly higher ESS scores in men, there was no gender difference in the association between disease severity and daytime sleepiness [17]. In other words the higher the AHI, the higher the likelihood of daytime sleepiness, regardless of gender. In 2004, Baldwin *et al.* [18] (also assessing the Sleep Heart Health Study sample) compared the methods employed by Young and Gottlieb, and found that ESS scores were higher in men. However, the authors also found that, despite ESS scores within normal limits, women often reported daytime tiredness—as in the Young *et al.* study. According to the author, men and women perceive sleepiness differently, and the ESS would be more appropriate for assessment of males. Clinical studies also demonstrate that obesity without sleep apnea is also associated with a higher prevalence of hypersomnolence [19].

In our sample, there were no significant between-gender differences in ESS score (10.13 ± 4.64 vs. 10.74 ± 5.15 points, $p = 0.379$). It bears noting that obesity per se causes sleepiness, regardless of the presence or absence of OSA [20]; as our sample was composed exclusively of obese individuals, this may account for the similarity in scores. Resta *et al.* reported similar findings in a study restricted to obese individuals [9].

In terms of social habits, alcohol intake was significantly associated with male gender (33.88% vs. 11.34%, $p < 0.0001$), whereas smoking was equally prevalent in both genders (9.84% vs. 8.25%, $p = 0.6852$).

Despite clear evidence of the association between hypertension and obesity and OSA alike [21], there is no well-established gender association. Some studies lend support to the hypothesis that inadequate sleep plays a role in the etiology of hypertension some young women, however, as a partial mediator of this relationship [22].

In our sample, hypertension was the most common comorbidity in both genders, with no statistically significant differences. These findings are consistent with those reported by Peppard *et al.* [21] in their 4-year assessment of Wisconsin Sleep Cohort Study participants (the authors found no gender differences). Conversely, Mohsenin *et al.* [23], studying patients from the Yale Sleep Cohort Study, found similar results in the sample as a whole, but stratification by BMI quartile revealed that men with higher BMI are at greater risk of hypertension than BMI-matched women.

Experimental laboratory studies have demonstrated that decreasing either the amount or quality of sleep decreases insulin sensitivity and decreases glucose tolerance [24]. Population-wide, the incidence of diabetes mellitus is slightly higher in women than in men [25]. A longitudinal study by Celen *et al.* [26] found a significantly higher incidence of type 2 diabetes in females than among males in a sample of 261 obese adults with OSA followed over a 16-year period. This finding is consistent with ours; in the present study, the presence of type 2 diabetes was significantly associated with female gender (29.00% vs. 9.49%, $p = 0.0132$).

Hypothyroidism is quite common in the population as a whole, and the prevalence of OSA is generally higher in patients living with this condition (25% to 35%). Glycosaminoglycan and protein infiltration of the tongue and pharynx, as well as neuropathy-induced changes in the pharyngeal dilator muscles, are considered plausible causes of the increased prevalence of OSA in hypothyroid patients. There have been scattered reports of regression of OSA after thyroxine replacement therapy [27]. The miss of the diagnosis of OSAS (in hypothyroid patients) may lead to an increased morbidity and mortality due to the well-known increased cardio-vascular risk of this syndrome [28]. In our sample, there was a clear association between hypothyroidism and female gender

(20.00% vs. 2.19%, $p < 0.0001$).

Depression was also significantly associated with female gender in our sample, although its prevalence was exceptionally high in males as well (80% vs. 63%, $p < 0.0001$). The population-wide prevalence of depression ranges from 5.8% to 8.4% (higher in those living with chronic illness—9.4% to 12.9%). Rezaeitalab *et al.* [29] also suggest it is more likely that OSAS patients present with anxiety and depression than the typical symptoms. In the general population, depression is usually more prevalent in women [30]; this pattern held true in our sample.

COPD affects 5 to 15% of adults (particularly those above the age of 50) in industrialized countries. It tends to predominate among men and smokers, with 65% of the latter developing COPD after the age of 65. Studies suggest that the prevalence of OSA in people with COPD is in the region of 14%, and that the prevalence of COPD in those with OSAHS is approximately 11% [31]. Smith *et al.* found that COPD was more strongly associated with female gender [32]. In our sample, however, we found no significant gender differences in COPD prevalence (1.38% in women vs. 0.73% in men, $p = 1.0000$). This may have been due to the low overall prevalence of the condition in our sample, which was itself a consequence of the age range of our participants.

Obstructive sleep apnea (OSA) occurs more commonly in asthma patients than in the general population and can complicate asthma management [33]. Sheperdycky *et al.* analyzed a sample of 130 males and 130 females with similar mean age (48.02 vs. 47.58 years) and BMI (40.41 vs. 40.05 kg/m²) and found a significant association between asthma and female gender [34]. In our sample, however, there were no significant gender differences, despite a substantial overall prevalence of asthma (18.62% vs. 21.90%, $p = 0.4934$). Guven *et al.* [33] also revealed no significant relationship between the presence of OSA and the clinical features of asthma, all patients with asthma should be evaluated for OSA.

In our PSG-based assessment of sleep architecture, one surprising finding was a higher LAT_{REM} in women (146.5 ± 85.93 min vs. 122.30 ± 68.28 min, $p = 0.0210$), despite their higher prevalence of depression. Shortened latency to REM sleep, a textbook marker of depression, would have been the expected finding. Nevertheless, Armitage *et al.* [35] also failed to find any significant between-group differences in LAT_{REM} in their comparison of clinical presentation and PSG parameters in subjects with a diagnosis of depression versus normal controls. Our findings were similar to those reported by Silva *et al.* [36], who also found a higher LAT_{REM} in women despite not restricting their sample to obese subjects.

Unlike Resta *et al.* [9], who found strong evidence of worse sleep fragmentation in obese women than in obese men, we found more severe sleep fragmentation (as measured by the number of microarousals) among male subjects (38.37 ± 27.44 vs. 28.07 ± 21.23, $p = 0.0017$). O'Connor *et al.* [37] conducted a gender comparison of sleep fragmentation and found that women had a significantly lower rate of microarousals than men during NREM sleep, but a similar arousal index during the REM stage. This sleep pattern was consistent with the predominance of apnea and hypopnea during REM sleep among women in the sample analyzed by the authors.

Regarding the differences of sleep stages between genders, researches showed that REM sleep seems to have the most adverse influence especially in women. There are few data defining the influence of slow-wave sleep in OSAS, but there are studies that describe the OSA severity is lower during the slow-waves [38].

In our data, the %Delta was low in both groups, it was significantly higher among women than in men (10.09 ± 7.48 vs. 7.55 ± 6.57, $p = 0.0037$), as reported by Valencia-Flores *et al.* [39]. These changes confirm previous findings that suggest a reduction in slow-wave sleep occurs in obese individuals [7] [8]. However, our findings suggest that, in women, other factors must be involved for BMI to be higher than in men.

Finally, as reported by other authors [2], the AHI was significantly higher in males than in females (30.56 ± 27.52 vs. 17.31 ± 18.54, $p < 0.0001$) as well as in other publications that women have a lower AHI than men during certain stages of sleep [40].

There were no significant gender differences in any of the other sleep pattern variables assessed (LAT, %REM, SAT_{MIN}, T90).

5. Conclusions

The present study detected gender differences both in the sleep patterns and in the comorbidities of patients with OSA. Men had a larger neck circumference, higher apnea and sleep fragmentation scores, were more likely to consume alcohol, and were more likely to have a history of myocardial infarction than women. Conversely, women tended to be more obese and were more likely to have comorbid diabetes mellitus, hypothyroidism, and

depression.

Knowledge of the distinct gender differences in OSA, such as obesity and its associated comorbidities contribute to a greater awareness of the disease, early diagnosis and its therapeutic management. However, further research should be conducted to verify the correlation of the most significant clinical findings and draw a profile of predictive factors, scaling the age and gender.

A limitation of this study is the sample size investigated. A greater number of samples can ensure a representative distribution of the population and thus be considered representative.

Conflict of Interests

The authors declare that they have no conflict of interests.

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