Received: 13 July 2017 | Revised: 22 November 2017 | Accepted: 5 December 2017

DOI: 10.1111/crj.12754

ORIGINAL ARTICLE

WILEY

Prevalence of comorbidities in patients with obstructive sleep apnea syndrome, overlap syndrome and obesity hypoventilation syndrome

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Abstract

Introduction: Sleep-disordered breathing causes a burden to the sufferer, the health care system and the society. Most studies have focused on obstructive sleep apnea (OSA); however, the prevalence of comorbidities in patients affected by overlap syndrome (OS) and obesity hypoventilation syndrome (OHS) has not been carefully evaluated.

Study objectives: The principal aim of this study was to identify the presence of comorbidities in patients suffering from OSA, OS, OHS and the differences in three groups of patients. Another purpose was to verify if sleepiness is associated with a greater prevalence of comorbidities.

Methods: A retrospective analysis in 989 adults referred for sleep diagnostic testing to our sleep center was performed. Patients were classified in OSA (721), OS (123) and OHS (145).

Results: The prevalence of comorbidities was higher in patients affected by OS and was the highest in the OHS group, while the prevalence of arterial hypertension is the highest in patients affected by OS. The probability of having more than two comorbidities follows the same trend. Excessive daytime sleepiness was associated with an increased rate of arterial hypertension, diabetes mellitus and the presence of multimorbidity in each group of patients.

Conclusions: The presence and the association of comorbidities seem to be higher in patients suffering from OSA, OS and OHS. Subjects suffering of OHS present a high prevalence of main diseases despite their younger age compared with others patients with SDB. Sleepiness may have a role, at least in a subset of these patients, into the development of comorbidities.

KEYWORDS

COPD, obesity, obstructive sleep apnea, oxidative stress, pathology, sleep apnea, sleep disorders

1 | INTRODUCTION

The prevalence of obstructive sleep apnea (OSA) is estimated at about 4%-7% in women and 9%-14% in men,[1,2] but a recent study in Switzerland population, applying the definitions more widely used in clinical sleep laboratories, reported that at least 23% of women and 49% of men had moderate-to-severe OSA.[3] OSA has been independently associated with metabolic and cardiovascular diseases, as well as significant comorbidities and health care resource utilization compared to controls.[4]

However, OSA is only the tip of an iceberg among the different types of sleep disordered breathing (SDB).[5] There are at least two that are frequent in the general population and deserve the same attention: the coexistence of OSA and COPD in the same individual, defined 'overlap syndrome' (OS) and obesity hypoventilation syndrome (OHS).

OS was identified by David Flenley almost 30 years ago and occurred in at least 3% of the European population affected by mild COPD[6] and is characterized by worse prognosis compared to COPD or OSA alone.[7]

OHS is a common condition characterized by the presence of hypoventilation while the subject is awake and is defined as the presence of obesity (BMI $\geq$ 30 kg/m^2) associated with daytime hypercapnia (pCO_2 > 45 mm Hg) in the absence of other causes of hypoventilation.[8,9] This syndrome is distinguished from classical OSA, in which patients have normal alveolar ventilation when awake, although the two conditions may frequently overlap. In fact, 70%-90% of patients with OHS also exhibit OSA, while 10%-15% of sleep apnea patients referred to sleep Laboratories have diurnal hypercapnia and can be classified as OHS.[10]

In OSA, OS and OHS, chronic intermittent hypoxemia during respiratory events may result in cardiovascular (CV) disorders by causing autonomic dysfunction,[11] endothelial dysfunction,[12] early microcirculatory impairment,[13] systemic inflammation,[14] oxidative stress, inflammation[15] and metabolic dysregulation.[16]

Previous studies have shown the relationship between SDB and many cardiovascular diseases such as arterial hypertension[17] and cardiac arrhythmias.[11] Moreover, OSA, OS and OHS are highly correlated with risk factors for coronary artery disease (CAD) including obesity, diabetes mellitus (DM), dyslipidemia and atherosclerosis.[18]

The main objectives of this study was to assess the prevalence of the main comorbidity at the time of first diagnosis of SDB in patients referred to Sleep Laboratory and to compare the presence of comorbidities in OSA, OS and OHS. Moreover, the presence of multimorbidity and the role of sleepiness in the various categories of SDB were evaluated.

2 | MATERIALS AND METHODS

The data of all consecutive patients who were referred to the Sleep Laboratory of the Institute of Respiratory Diseases of the University of Foggia and the Sleep Center of Fondazione Maugeri of Cassano delle Murge in the last 5 years were collected.

All patients underwent unattended cardio-respiratory overnight monitoring (Vitalnight 11; Rangendingen, Germany) in the sleep laboratory. Oro-nasal flow was measured by a nasal cannula, whereas abdominal and rib-cage movements were measured by pneumatic sensors, while oxyhemoglobin saturation was assessed with a finger probe (this is quite different to standard AASM criteria, which needs thermistor, and the hypopnea definition is bit different). A manual analysis was performed the day after registration by a physician specialized in sleep disorders according to standard criteria. In summary, obstructive apnea was defined as a reduction of the flow at 90% at least for 10 seconds with the presence of abdominal or thoracic movement, central apnea in absence of both, hypopnea was identified when there was 50% reduction of flow for 10 seconds or more, followed by a decrease in oxygen saturation of 4%. AHI was defined as the number of apneas plus hypopneas divided by the registration time (hours), and oxygen desaturation index (ODI) was the number of desaturation >4% divided by the registration time (hours). All patients underwent spirometry and blood gas analysis and thus, according to the results of these exams, were divided into three groups: OSA (no obstructive pulmonary disease, $PaCO_2$ below 45 mm Hg); OS (presence of obstructive pulmonary disease at spirometry in case of a post-bronchodilator FEV1/FVC ratio of <0.7) associated with obstructive sleep apnea) and OHS (BMI >30, diurnal alveolar hypoventilation with $PaCO_2$ higher than 45 mm Hg in the absence of other possible causes of hypoventilation).

The factors of age, BMI index, sex and smoke habits were considered for each patient.

The Epworth Sleepiness Scale was used to measure sleep propensity.

During the patient's first visit, using a questionnaire, data regarding the presence of comorbidities were collected with focus on arterial hypertension, heart disease (arrhythmias, heart failure, history of ischemic diseases, etc), endocrinopathies (diabetes mellitus and thyroid disorders in particular) and the presence of metabolic syndrome.

Finally, patients with heart failure history or neuromuscular diseases were excluded from the study.

2.1 | Statistical analysis

Distribution of demographic data and prevalence of comorbidities for each SDB are presented by descriptive statistics. The chi-square test (χ^2) was used to assess the relationship between two categorical variables. To examine differences

TABLE 1 General characteristics of patients[a]

	OSAS	OS	OHS	*P*
Number of patients (% pred)	721 (70.9%)	123 (12.4%)	145 (14.6%)	
Male (% pred)	73	80	66	.02
Age (years)	58.68 ± 13.30	65.18 ± 10.70	58.49 ± 13.81	<.001
BMI (kg/m^2)	34.67 ± 7.83	33.32 ± 7.23	41.55 ± 8.61	<.001
ESS	12.26 ± 5.94	9.49 ± 5.32	14.43 ± 5.45	<.001
Current smoker (% pred)	34	39	49	<.001
FEV1 (% pred)	94.18 ± 19.38	67.19 ± 17.76	78.22 ± 20.87	<.001
FVC (%pred)	95.74 ± 18.42	86.05 ± 17.36	80.25 ± 19.80	<.001
FEV1/FVC	80.54 ± 6.31	59.08 ± 9.40	79.88 ± 7.79	<.001
AHI (events/hour)	45.23 ± 24.76	42.69 ± 23.74	60.13 ± 28.33	<.001
ODI (events/hour)	42.36 ± 25.78	40.05 ± 23.65	60.55 ± 29.75	<.001
T90 (%TIB)	26.55 ± 27.94	30.85 ± 30.30	54.40 ± 29.66	<.001
PaO2 (mm Hg)	78.98 ± 11.49	71.37 ± 11.36	66.63 ± 9.49	<.001
PaCO2 (mm Hg)	39.11 ± 3.78	40.65 ± 5.24	49.02 ± 4.12	<.001
pH	7.42 ± 0.03	7.42 ± 0.03	7.40 ± 0.03	<.001

[a]Results are presented as mean ± SD.

among the three groups, one-way analysis of variance (ANOVA) was performed.

A multivariate logistic regression analysis was performed to calculate the odds ratios among patients with sleepiness (ESS ≥ 10) and comorbidities. A *P* value of <.05 was considered to be significant. The results are presented as OR with 5% to 95% CI and *P* values. The data were analyzed by the Statistical Software (GraphPad 6.01, 2012; GraphPad Software Inc., La Jolla, USA).

3 | RESULTS

According inclusion criteria, 989 subjects were included in the study. Among these, OSA was the most frequent sleep disorder present in our population (70.9%), while OS and OHS had about the same incidence (12.4% and 14.6%, respectively). Patients with OS were older than in other groups. In all groups, patients were obese or almost overweight. As aspect, OHS had a morbid obesity. By definition OS had poor respiratory function with lower FEV1/FVC and lower FEV1. Regarding sleep parameters, patients with OHS had higher AHI, ODI and T90% (time with saturation below 90%). Gas exchange was worse in OHS with lower PaO_2 and higher $PaCO_2$ than in other groups (Table 1).

With respect to comorbidities, arterial hypertension was the most frequent disorder in all groups, with a range from 59.5% in OSA to 82% in OS in all groups. Diabetes mellitus and heart diseases were also very common and were found in one-third of the patients, with higher prevalence in OHS. Metabolic syndrome was found in 13% of OSA and in 22% of OS, and an even higher percentage was observed in OHS (25%). Other comorbidities were present in each group. Finally, it is interesting that a high percentage of patients had three or more associated comorbidities, and this is particularly

TABLE 2 Prevalence of main comorbidities in each type of sleep disordered breathing

	OSAS	OS	OHS	*P*
Arterial hypertension (% pred)	59.5	82	73.5	.02
Heart diseases	29	28	34	.53
Diabetes mellitus	19,5	24	40	<.001
Dysthyroidism	13	13	20	.09
Dyslipidemia	24	28	26	.90
Others	16	9	13	.28
Metabolic syndrome	13	22	25	<.01
≥3 comorbidity	16	32	32	<.001

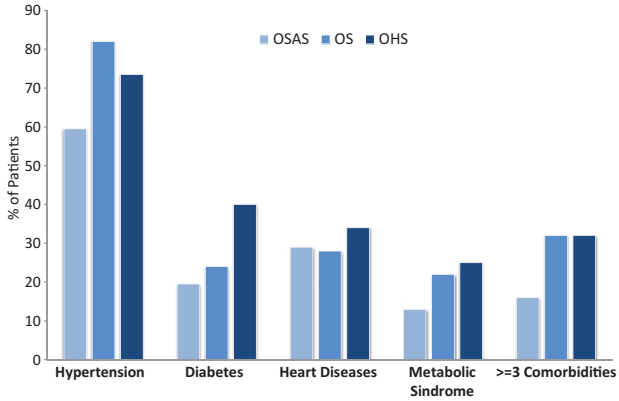

FIGURE 1 Prevalence of main comorbidities in OSAS, OS and OHS

true in patients with OHS or OS in which almost 1/3 of them had more than three comorbidities (Table 2 and Figure 1)

The presence of self-reported sleepiness (ESS $\geq$ 10) proved an increased risk factor of comorbidities.

Table 3 shows the prevalence of the main comorbidities in each group of sleep-related disorders (SRD), divided according to the presence or absence of sleepiness. As demonstrated, symptomatic patients for sleepiness had in general a higher prevalence of arterial hypertension, diabetes mellitus, metabolic syndrome, and frequently had three or more comorbidities associated. In Table 4 and Figure 2, odd ratios were shown, demonstrating statistical significance only for an increased risk for diabetes in OSAS and a higher risk for three or more comorbidities in OS.

4 | DISCUSSION

According to the results of this study, it is possible to describe a number of interesting observations. First of all, patients who suffered from sleep disordered breathing have a greater prevalence of comorbidities, in particular heart diseases and metabolic disorders. Moreover, patients affected by any kind of SDB have a higher tendency to develop comorbidities when symptomatic for daytime sleep propensity.

A recent larger study found a significant prevalence of comorbidities in patients with OSA compared to healthy controls, which increased with ageing and was also influenced by sex.[19]

TABLE 4 Odd ratio of sleepiness for main pathology into different SRD

	OR	CI 95%	*P*
OSAS			
Arterial hypertension	1.35	0.87-2.09	.17
Diabetes mellitus	2.83	1.63-4.91	<.001
≥3 comorbidities	1.36	0.75-2.45	.30
Metabolic syndrome	1.11	0.59-2.09	.73
OS			
Arterial hypertension	3.13	0.59-16.59	.16
Diabetes	2.31	0.64-8.22	.18
≥3 comorbidities	3.41	0.97-11.93	.049
Metabolic syndrome	1.73	0.43-6.98	.43
OHS			
Arterial hypertension	0.71	0.23-2.17	.54
Diabetes	2.20	0.77-6.23	.13
≥3 comorbidities	1.48	0.51-4.21	.46
Metabolic syndrome	1.86	0.38-9.10	.43

It is well known that patients with OSA present an increased risk to develop comorbidities, which usually begins several years before clinical diagnosis of OSA.[20–23]

The association between OSA and COPD (OS) is estimated around one in 160 of the general population over the age of 40 years, and it is also known that patients with OS have increased sleepiness, lower total sleep time, lower sleep efficiency and a higher arousal index compared to those with COPD alone,[24] but few data are available about the complications of this syndrome. Our data confirm that OS are usually older that OSA and OHS patients; nevertheless, except arterial hypertension, they have almost the same prevalence of comorbidities as in OSA, while prevalence of diabetes mellitus is lower compared to OHS. These data seem to suggest that in OS, prevalence of comorbidities is more influenced by age (or maybe by COPD) than by apnea itself, while there is a direct relationship with sleep disorder, which became important in OSA and even more in OHS subjects.

It has been reported that patients with OHS have a higher mortality rate than in obese patients without OHS (23% vs 9%; hazard ratio: 4.0).[25] In a small cohort of patients, it has been demonstrated that subjects with OHS have greater cardiorespiratory comorbidities, higher hospitalization and

TABLE 3 Prevalence of comorbidities according to the presence of sleepiness

	Arterial hypertension		Metabolic syndrome		Diabetes mellitus		≥3 comorbidities	
	ESS ≤ 10	ESS > 10	ESS ≤ 10	ESS > 10	ESS ≤ 10	ESS > 10	ESS ≤ 10	ESS > 10
OSAS	56	63	12	14	16	23	14	18
OS	74	90	16	25	16	40	19	45
OHS	78	69	16	30	26	42	30	34

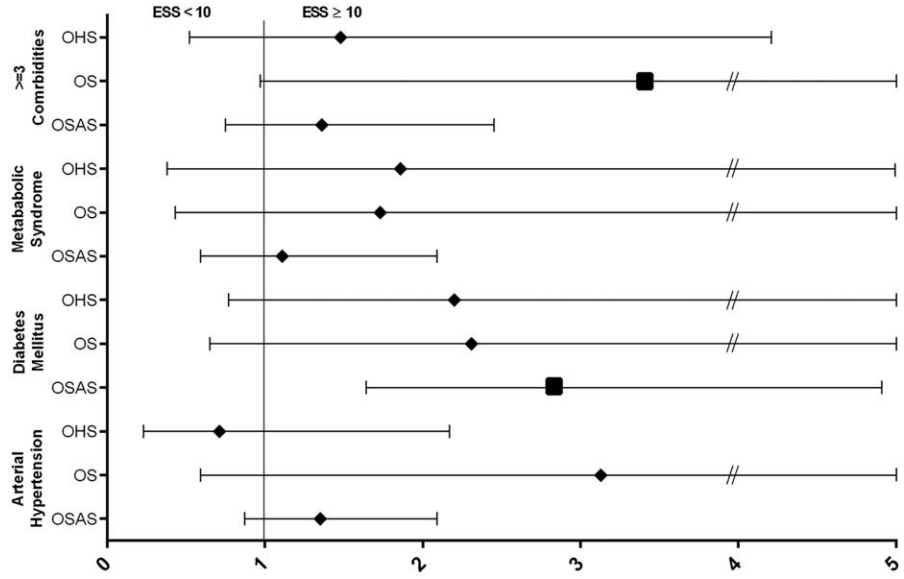

FIGURE 2 OR for main comorbidities in different SDB according sleep propensity (evaluated by Epworth Sleepiness Scale). Subjects with sleepiness have a general trend to develop arterial hypertension, diabetes mellitus, metabolic syndrome and multimorbidity, but only in two cases, OR is statistical significant (square point)

health care utilization.[26] The results of the present study, in a large study population, demonstrated that patients with OHS, even if they are usually younger, have high prevalence of comorbidities. OHS has different factors, which can justify these results: morbid obesity, higher level of oxidative stress and chronic inflammation, alteration of sleep quality and gas exchange.[10] These conditions, put all together, create a deleterious cocktail, which contribute to increase cardiovascular and metabolic risk. Thus, if we consider that it is estimated that approximately 6% of the general US population has BMI $\geq$40 kg/m^2, probably more than half of them have OSA and consequently approximately 20% of these OSA patients have OHS.[27] In our opinion, they are the real challenge for the future if we want to control health resources and costs associated with sleep disorders.

Smith et al reported an association between OSA and presence of multimorbidity.[22] Our data not only confirm the presence of multimorbidity in OSA patients but also demonstrate that in other SDB categories, there is a high prevalence of multimorbidity, and patients with OHS seem to be particularly affected by this phenomenon despite their younger age.

Presence of two or more chronic diseases, namely multimorbidity, is an emerging concept in medicine,[28] which leads to a reduction in quality of life and significant increase in health care resource utilization.[26] In an OSA population, Marrone et al demonstrated that age and comorbidities predicted all causes of mortality, independently of the severity of AHI or Nadir SaO_2.[29]

Moreover, OSA patients have a high number of health care contacts and health care usage[22] and a recent study confirms that several morbidities are present in patients with OSA or OHS at least 8 years prior to their SDB diagnosis.[4]

Up to day, it is not clear whether earlier diagnosis of SDB and subsequent timely treatment could reduce the incidence of comorbidities in the future. However, in some cases, for cardiovascular diseases, there is substantial evidence that nocturnal therapy can improve the incidence of cardiovascular risk, so we could speculate that early treatment of any kind of SDB may impact on the prevention of other comorbidities.

The relationship between sleepiness and comorbidities is another intriguing question. In fact, several factors such as obesity, metabolic abnormalities and inflammatory markers may play a role in the genesis of excessive daytime sleepiness.[30] Medeiros et al[31] have shown that excessive daytime sleepiness is common in type 2 diabetes, while our data confirm that excessive daytime sleepiness is independently associated with the prevalence of diabetes mellitus in the OSA population. This is in agreement with previous reports, which show that longer T90% and shorter sleep time increase the risk of diabetes mellitus,[32] and it is known that T90% is one the most important factors which can also influence diurnal PaO2.[33] The relationship between sleep and incidence of metabolic and cardiovascular diseases could be mediated by oxidative stress caused by intermittent hypoxemia as well as sleep deprivation (or sleep fragmentation), which increases sympathetic activation and alterations in hypothalamic–pituitary–adrenal axis.

Hence, even if the exact mechanisms are unknown, a bidirectional relationship between inflammation, sympathetic activation and sleep quality (fragmentation and sleepiness in particular) seems to be quite clear.

In conclusion, in this study, we better defined the possible relationship between different types of SDB and

prevalence of common comorbidities. Moreover, we emphasize the possible role of SDB in the development of multimorbidity, which was previously described only in OSA.[34] The study also underlines the association between sleepiness, comorbidities and multimorbidity.

4.1 | Limitations of the study

This is only an observational study. According to our results, it is not possible to conclude that early diagnosis and treatment of SDB can reduce consequences, in particular for patients with OHS. Nevertheless, even if use of CPAP has demonstrated a positive impact to reduce symptoms, cardiovascular morbidity and mortality, an improvement of screening procedures, changes in life style and weight reduction should be always desirable to prevent the main consequences of sleep related morbidity and mortality.

ACKNOWLEDGMENT

The work was performed at the Sleep Laboratory of the Institute of Respiratory Diseases of the University of Foggia (Viale degli Aviatori 1, 71122 Foggia) and the Sleep Center of Fondazione Maugeri of Cassano delle Murge (Contrada Frà Diavolo, 13, 70020 Cassano delle Murge BA).

CONFLICT OF INTEREST

All authors declare not to be involved in any financial interest or relationship with a commercial interest held by the individual or members of their family (spouses, domestic partners and dependent children) over the preceding 12 months. They are also not involved in any conflicts of interest and off-label or investigational use.

AUTHOR CONTRIBUTIONS

Designed research/study, performed research/study, collected data, analyzed data and wrote the paper: Lacedonia
Designed research/study: Carpagnano, Foschino Barbaro
Performed research/study and collected data: Patricelli, Carone
Analyzed data: Gallo
Collected data and wrote the paper: Caccavo
Collected data and analyzed data: Sabato
Collected data: Depalo, Aliani, Capozzolo

ETHICS

The study was approve by local ethics committee.

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How to cite this article: Lacedonia D, Carpagnano GE, Patricelli G, et al. Prevalence of comorbidities in patients with obstructive sleep apnea syndrome, overlap syndrome and obesity hypoventilation syndrome. *Clin Respir J*. 2018;12:1905–1911. https://doi.org/10.1111/crj.12754