Co-morbidities and sleep apnoea severity. A study in a cohort of Portuguese patients

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Introduction. Obstructive sleep apnoea syndrome (OSAS) is frequently associated to other morbid conditions that act as risk factors influencing OSAS morbidity and mortality.

Aim. To analyse the presence of co-morbidities in OSAS patients, recruited from a sleep outpatient clinic in Northern Portugal, stratified as a function of OSAS severity.

Patients and methods. A cohort of 319 sleep-disordered patients was assessed by clinical and sleep video-polygraphic recording. Patients (n = 209) with sleep respiratory distress had OSAS (n = 145) and severity defined according to Apnoea/Hypopnea Index (AHI); 64 had primary snoring or respiratory distress with AHI < 5; and 110 had other sleep disorders. A full individual background study was possible in 128 OSAS patients. The association to unique or multiple co-morbidities was assessed by clinical and analytical studies in general group or as a function of OSAS severity.

Results. The presence of co-morbidities was of 75% in all OSAS patients and of 79.5% in the severe group of OSAS. Forty seven of patients had only one co-morbidity. The most common was obesity (56.3%) followed by high blood pressure, diabetes and other cardiovascular disorders. Obesity was present in 84% among the most severe OSAS cases and always present in those with multiple co-morbidities. When compared with the group of patients without sleep respiratory distress the co-morbidity condition was more frequently related to OSAS (p = 0.0196).

Conclusion. Comorbidities are commonly associated to OSAS independently of disease severity. Among the comorbidities present obesity was the most common in the most severe OSAS cases.

Key words. Apnoea severity. Co-morbidity. Metabolic disorders. Obesity. Obstructive sleep apnoea syndrome. OSAS. Sleep disorders.

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Introduction

Obstructive sleep apnoea syndrome (OSAS) is a common and chronic disorder resulting from diverse aetiologies [1,2] frequently associated to other morbid conditions [3-6]. OSAS could occur in infancy, because of ear, nose or throat (ENT) dysfunction, lesions or abnormal development, but is more prevalent in adults, namely in men [1,8-13] or in women after menopause [1].

OSAS is characterized by repetitive episodes of pharyngeal collapse leading to apnoea (if collapse is total) or to hypopnoea (if partial) during sleep, although the respiratory effort is still present [2,7,8]. A decrease in amplitude of air flow higher than 50% is characteristic of apnoea and if it is between 25-50% is characteristic of hypopnoea [8].

Apnoea severity is defined according to an Apnoea/Hypopnoea Index (AHI) [8]: the number of apnoea or hypopnoea per hour.

The episodes of apnoea/hypopnoea are frequently associated clinical symptoms such as arousals, sleep fragmentation, among others [10,14-16] that could influence the existence of a rather general morbid condition [17,18]. Likewise, the degree of environmental influences on the development of OSA is unknown, but is undoubtedly considerable [1].

Besides these common varieties of symptoms that flourishes to clinical OSAS picture it is also frequent the association between OSAS and other clinical entities commonly recognised as Co-Morbidities (co-morbidities). In this respect, we can highlight that the metabolic syndrome (obesity, impaired glucose metabolism/insulin resistance, hypertension, hyper-triglyceridemia and lower high-density lipoprotein cholesterol, impotence and pro-inflammatory state) [10,19,20], as also cardiovascular disease [14] and cancer [21-23] are common OSAS co-morbidities. These co-morbidities may act as risk factors and influence the morbidity and mortality of individuals affected by OSAS [16,19].

Taking all these information into account, it is clear that the identification of co-morbidities in OSAS patients is necessary to define the clinical

picture and consequently to find the more adequate treatment. However, as the severity of the clinical condition (OSAS + co-morbidities) is influenced by the level of OSAS severity, this relationship needs to be well defined. This is why the present study addresses the association between OSAS and co-morbidities as a function of OSAS severity qualification/quantification, considering such severity as a factor that could influence the morbid condition. With better identification of the factors that aggravate the clinical condition the treatment could be better addressed, more complete and case specific.

The purpose of this study was to analyse the presence of co-morbidities in a cohort of OSAS patients, recruited in a sleep outpatient clinic from the Northern of Portugal, stratified as a function of OSAS severity and to analyse the possible influence of such severity on the clinical condition OSAS-co-morbidities.

Patients and methods

Sample

The study group consisted on the analysis of a cohort of 319 sleep disordered patients consecutively and prospectively assessed within a period of 10 months, for the first time coming to the Sleep Outpatient Clinic of the Hospital Santo António, Porto (North of Portugal). The research was conducted in accordance with Helsinki Declaration, approved by the Hospital Ethics Committee and included analysis of diverse patients characteristics [24].

Methods

Each patient underwent a standard overnight sleep laboratory polysomnography (PSG) study with video-polygraphic recording including EEG (electroencephalogram), EOG (electro-oculography), EMG (electromyography), ECG (electrocardiogram), nasal and thoracic respiration, O_2 saturation, and movement and behaviour to document sleep parameters and sleep architecture. PSG variables and AHI severity (mild AHI 5-15; moderate > 15-30; severe > 30) were defined accordingly to standards [8,25].

The prevalence of co-morbidities was assessed by clinical and analytical studies and grouped on the following entities: obesity (as a function of Body Mass Index (BMI) > 30, according to WHO [26]), diabetes, high blood pressure (HBP), cardiovascular/vascular, neurological, muscle-skeletal disorders, cancer, ENT disorders and upper airway respiratory disorders, psychiatric disorders. All these co-morbidities were also analysed as a function of OSAS severity sub groups.

Differences in the between groups were assessed using chi-square test and values of $p < 0.05$ to indicate those statistically significant.

Results

From the initial cohort of 319 sleep disordered patients (226 M, 93 F) consecutively evaluated by clinically and sleep EEG recording, 209 had sleep respiratory distress (OSAS or other) and 110 (53 M, 57 F) had, according to ICSD3 [8], sleep disorders without respiratory distress. From this last group 46 patients (22 M, 24 F) had periodic limb movement, 18 (8 M, 10 F) insomnia, 9 (3 M, 6 F) narcolepsy or other hypersomnia, 6 (1 M, 5 F) parasomnia, 6 (4 M, 2 F) other sleep disorders, and 25 had no specific sleep alteration.

Of the group of sleep respiratory distressed patients (n = 209; 173 M, 36 F), 64 (45 M, 19 F) had primary snoring or snoring and respiratory distress with an AHI < 5, and 145 (128 M, 17 F) fulfill the sleep polygraphic criteria for OSAS. A full study of individual background was only possible in 128 patients. The group of 128 patients with OSAS was fully assessed for the presence/absence of co-morbidities.

For purposes of results comparison the group of 110 non-respiratory distressed patients underwent the same assessment.

Co-morbidities

Table I provides a description of the sample according to the gender, age and severity of OSAS. The majority of patients were male, with mild or moderate apnoea. The cohort of 128 OSAS patients (111 M, 17 F) has a mean age of 54.6 years (Table I). The distribution by gender of the 96 OSAS patients with co-morbidities follows the same proportion as the general OSAS population, in which the majority of patients were males (Table I). Considering the severity subgroups the distribution was also similar to the general group. The majority of patients belong to mild or moderate apnoea severity (Table I).

Co-morbidities were present in 75% of OSAS patients vs 61% in non-respiratory distressed patients. The OSAS-co-morbidities relationship was higher (79%; 31/39 patients) in severe (AHI > 30) apnoea cases. However, no significant difference between the OSAS severity subgroups was found (p =

0.739). Among the co-morbidities found in OSAS patients, obesity was the most frequent one followed by HBP, diabetes, cardiovascular diseases and psychiatric disorders (Table II). If we consider the subgroups of OSAS severity and compare distribution of the co-morbidities between them, it is possible to check that obesity is present into 84% (26/31) of the patients with severe apnoea. HBP was present in all OSAS severity sub-groups and as cardiovascular/vascular disorders they are also the most common in non-respiratory distressed patients. Differences among severity OSAS subgroups are not statistically significant. Cancer is a co-morbid condition only present in mild or moderate AHI subgroups in our population (Table II).

The association between the number of co-morbidities and OSAS severity was assessed by comparing the number of co-morbidities to apnoea severity (Table III). Approximately half (47%) of all OSAS patients with co-morbidities, presented only one co-morbidity. Obesity was the most common. The remaining 53% showed multiple co-morbidities. Again, obesity was one of the two main co-morbidities. The other one was HBP. Both (obesity and/or HBP) were associated to other co-morbidities in all groups but more frequent in more severe apnoea cases (Table III). Although the occurrence of multiple co-morbidities was higher in the mild and moderate AHI subgroups than in the severe subgroup, the differences were not significant ($p = 0.405$).

The relationship between co-morbidities and sleep disorder in the groups of patients studied was assessed by comparing the presence/absence of co-morbidities in the group of OSAS patients vs. the group of patients with non-respiratory distressed. Differences in frequencies between groups were assessed using chi-square test and values of $p = 0.0196$ indicate that the co-morbid condition was more frequently related to OSAS.

Table I. Distribution of patients with OSAS (AHI > 5) and with co-morbidities as a function of OSAS severity.

		Mild (AHI 5-15)	Moderate (AHI > 15-30)	Severe (AHI > 30)	OSAS (Total)
OSAS patients	Total	59 (46%)	30 (23%)	39 (31%)	128
	Males	47 (42%)	29 (26%)	35 (32%)	111 (87%)
	Females	12 (71%)	1 (5%)	4 (24%)	17 (13%)
Mean age (years) of OSAS patients	Total	54.1	53.8	56.1	54.6
	Males	53.1	53.9	56.8	54.5
	Females	57.8	51.0	49.5	55.5
OSAS patients with co-morbidities	Total	43 (45%)	22 (23%)	31 (32%)	96 (75%)
	Males	31 (39%)	21 (26%)	28 (35%)	80 (83%)
	Females	12 (75%)	1 (6%)	3 (19%)	16 (17%)
Mean age (years) of OSAS patients with co-morbidities	Total	55.8	54.3	57.1	55.9
	Males	55.0	54.4	58.3	56.0
	Females	57.8	51.0	46.0	55.2

AHI: Apnoea/Hypopnea Index per hour of sleep; OSAS: obstructive sleep apnoea syndrome.

Discussion

Morbid conditions associated with sleep pathologies are rather common and can be the reason why diverse sleep disorders have so varied semiology. OSAS is an example of a common sleep pathology that is frequently associated to other morbid conditions and, among these, those described as co-morbid 'metabolic' entities. These entities, namely obesity, cardiovascular disturbances or diabetes are part of the 'metabolic burden' which may be largely influenced by genes that have an effect on insulin resistance and body fat distribution, aggravating OSAS picture and actively interfering with sleep structure, which suggests that OSAS may be part of a 'metabolic' syndrome [27]. However, and even if OSAS is considered a clinical entity associated with 'metabolic syndrome', a recent and extensive meta-analysis of cross-sectional and case-control studies failed to 'prove a causality between these two factors' [28].

Obesity is the most documented co-morbidity and major risk factor of the 'metabolic burden' for OSAS [10] in adults [20] or in children [1,20]. The mechanism suggested appears to be the reduction of nasopharyngeal caliber, secondary to fat deposition in upper airway tissues and/or as a result of hypoventilation due to a decrease in chest wall compliance [1,10]. It is also known that weight loss may reduce the severity of the condition [10]. In the present study we analysed the association and the influence of those co-morbidities on the aggravation of the OSAS.

To test the influence of such co-morbidities, we compare their presence in patients with OSAS to a sample of patients without respiratory distress, assessed from our initial cohort. We also compared our findings to the occurrence such co-morbidities

Table II. Patients with OSAS (according to severity) or with non-respiratory distress having co-morbidities.

	OSAS				Non-respiratory distressed (*n* = 67)
	Mild (*n* = 43)	Moderate (*n* = 22)	Severe (*n* = 31)	Total (*n* = 96)	
Obesity (BMI > 30)	19 (44%)	9 (45%)	26 (84%)	54 (56%)	12 (18%)
High blood pressure	17 (39%)	7 (32%)	10 (32%)	34 (35%)	15 (22%)
Diabetes	8 (18%)	4 (18%)	5 (16%)	17 (18%)	7 (10%)
Cardiovascular and vascular disorders	9 (21%)	1 (5%)	5 (16%)	15 (16%)	16 (24%)
Psychiatric disorders	6 (14%)	2 (9%)	1 (3%)	9 (9%)	8 (12%)
Muscle-skeletal disorders	4 (9%)	3 (14%)	2 (6%)	9 (9%)	10 (15%)
Neurological disorders	4 (9%)	2 (9%)	2 (6%)	8 (8%)	5 (7%)
Cancer	3 (7%)	5 (23%)	–	8 (8%)	7 (10%)
ENT and other upper airway respiratory disorders	4 (9%)	2 (9%)	2 (6%)	8 (8%)	6 (9%)
Blood pathology	3 (7%)	3 (14%)	–	6 (6%)	4 (6%)
Miscellaneous	4 (9%)	2 (9%)	2 (6%)	8 (8%)	11 (16%)

The total number of co-morbidities is higher than the number of patients because each one can have more than one. BMI: Body Mass Index; ENT: ear nose and throat; OSAS: obstructive sleep apnoea syndrome.

Table III. Presence of one or multiple (most common) co-morbidities in OSAS patients according to apnoea severity.

	Mild (*n* = 43)	Moderate (*n* = 22)	Severe (*n* = 31)	OSAS (*n* = 96)
Only one co-morbidity	17/45 (38%)	11/45 (24%)	17/45 (38%)	45/96 (47%)
Obesity	5/17 (29%)	3/11 (27%)	12/17 (71%)	20/45 (44%)
Multiple co-morbidities	26/51 (51%)	11/51 (22%)	14/51 (27%)	51/96 (53%)
Obesity + HBP + other	5/26 (19%)	5/11 (46%)	8/14 (57%)	18/51 (35%)
Obesity + other (not-HBP)	9/26 (35%)	1/11 (9%)	6/14 (43%)	16/51 (31%)
HBP + other (not-obesity)	11/26 (42%)	2/11 (18%)	–	13/51 (26%)
Others (not HBP neither obesity)	1/26 (4%)	3/11 (27%)	–	4/51 (8%)

HBP: high blood pressure; OSAS: obstructive sleep apnoea syndrome.

in the population assessed by a national inquiry, from INE, 2014 [29] and from other cohorts from the same Portuguese origin [30,31].

In both populations, non-respiratory distressed patients and population inquired, the co-morbidities found have different relevance with obesity behind HBP (or other cardiovascular disorders). The same finding was present on the less severe OSAS cases (AHI < 30) that are more frequently associated to other comorbidities than obesity.

The analysis of data from the Portuguese nationwide health inquiry show that more than a half of adults (> 18 years old) were overweight, with increased evidence in women when compared with the previous inquiry from 2005-2006 [29]. Also Do Carmo et al [30] reported 53.6% of population were obese or overweight. Considering those having obesity (BMI ≥ 30) the value drops to 14.2%. In the 2014 inquiry HBP was found in 25.3%; diabetes in 9.3%; depression in 11.9% and cardiac and cerebrovascular disorders in 7.9%, as the most common disorders. The epidemiological study of Macedo et al [31] in a cohort of 5023 adults (> 18 up to 90 years old and with 2737 women) the prevalence of HBP was of 42.1% (higher in the age group 35-64 years old).

When we look for the results expressed in table II, OSAS patients had higher prevalence of obesity, HBP, diabetes, cardio and vascular disorders, than the general population stressing that the rate of association of co-morbidities (mainly included on the 'metabolic burden') is common and is significantly higher in OSAS patients when compared to non-sleep respiratory distressed patients.

In this study we also tested if the co-morbid condition was influenced by OSAS severity (determined by the AHI). The finding that co-morbidities are more frequent in more severed apnoea patients does support such hypothesis.

When co-morbidities were ranked by frequency, obesity is the most common and more frequently associated to OSAS and within the group of multiple co-morbidities in the most severe OSAS cases obesity is always present (Table III). When obesity is taken apart no patients with severe OSAS were found (Table III), and when multiple co-morbidities are present the influence of obesity is less impressive. These results support the hypothesis that obesity is the most common comorbidity in OSAS having a role on the severity of this condition.

Taking altogether, these findings clarify the understanding of the relationship between co-morbidities/OSAS and vice versa. In one way, because co-morbidities are frequent in populations from the same origin and with similar age, as in our less severe apnoea cases the occurrence of OSAS can negatively influence the course of such co-morbid entities. In the other way, obesity is the comorbidity that

exacerbates OSAS severity. This has immediate influence on the sleep structure and consequently it deteriorates the 'metabolic burden' of patient condition.

In conclusion, the present study of the relationship between co-morbidities and OSAS (by the first time reported in a Portuguese sample), confirms that at the time of sleep disorder diagnosis co-morbidities mainly those associated or included on the 'metabolic burden' are common, independently of OSAS severity. From our results is also possible to conclude that obesity is a common condition in severe cases and plays a major role on sleep apnoea aggravation.

The findings of this common association of co-morbidities in non-severe cases of OSAS, and of the role of obesity on apnoea aggravation, have strong clinical implications on patient health deterioration, as a result of the increasing of apnoea severity and failure of the 'metabolic' condition.

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Comorbilidades y gravedad de la apnea del sueño. Estudio en una cohorte de pacientes portugueses

Introducción. El síndrome de apnea obstructiva del sueño (SAOS) se asocia frecuentemente a otras enfermedades que actúan como factores de riesgo que influyen en la morbilidad y mortalidad del SAOS.

Objetivos. Analizar la presencia de comorbilidades en pacientes con SAOS, seleccionados en una clínica del sueño ambulatoria en el norte de Portugal y clasificados atendiendo a la gravedad del SAOS.

Pacientes y métodos. Una cohorte de 319 pacientes con trastornos del sueño fueron evaluados mediante estudios clínicos y registro videopoligráfico durante el sueño. Del total de pacientes (n = 209) con distrés respiratorio durante el sueño, 145 tenían SAOS con gravedad definida según el índice de apnea/hipopnea (IAH); 64 presentaban ronquidos primarios o distrés respiratorio con IAH < 5; y 110 tenían otros trastornos del sueño.

Resultados. La presencia de comorbilidades fue del 75% en todos los pacientes con SAOS y del 79,5% en el grupo de pacientes con SAOS grave; 47 pacientes presentaban una única comorbilidad, la más común de las cuales fue la obesidad (56,3%), seguida de hipertensión, diabetes y otros trastornos cardiovasculares. La obesidad estuvo presente en el 84% de los casos más graves de SAOS y en el 100% de casos con múltiples comorbilidades. En comparación con el grupo de pacientes con distrés respiratorio durante el sueño, la comorbilidad aparece normalmente relacionada con el SAOS (p = 0,0196).

Conclusión. Las comorbilidades se asocian con frecuencia al SAOS, independientemente de la gravedad de la enfermedad. Entre las comorbilidades presentes, la obesidad resultó ser la más común en los casos más graves de SAOS.

Palabras clave. Comorbilidad. Gravedad de la apnea. Obesidad. SAOS. Síndrome de apnea obstructiva del sueño. Trastornos del sueño. Trastornos metabólicos.