Obstructive Sleep Apnea and Metabolic Syndrome in Spanish Population

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Abstract: Obstructive sleep apnea (OSA) is a clinical picture characterized by repeated episodes of obstruction of the upper airway. OSA is associated with cardiovascular risk factors, some of which are components of metabolic syndrome (MS).

Objectives: First, determine the prevalence of MS in patients with OSA visited in sleep clinic. Second, evaluate whether there is an independent association between MS components and the severity of OSA.

Methods: Patients with clinical suspicion of OSA were evaluated by polysomnography. Three groups were defined according to apnea hypoapnea index (AHI): no OSA (AHI <5), mild-moderate (AHI≥ 5 ≤30), and severe (AHI> 30). All patients were determined in fasting blood glucose, total cholesterol, HDL cholesterol, triglycerides and insulin. MS was defined according to criteria of National Cholesterol Education Program (NCEP).

Results: A total of 141 patients (mean age 54 ± 11 years) were evaluated. According to AIH, 25 subjects had no OSA and 116 had OSA (41mild-moderate and 75 severe). MS prevalence ranged from 43-81% in OSA group. Also, a significant increase in waist circumference, triglycerides, glucose, blood pressure levels, and a decrease in HDL cholesterol levels was observed in more severe OSA patients. All polysomnographic parameters correlated significantly with metabolic abnormalities. After a multiple regression analysis, abdominal obesity ($p < 0.02$), glucose ($p < 0.01$) and HDL cholesterol ($p < 0.001$) were independently associated with OSA.

Conclusions: Our findings show high prevalence of MS in OSA, especially in severe group. A significant association between OSA and some of the components of MS was found in Spanish population.

Keywords: Obstructive sleep apnea, metabolic syndrome, HDL cholesterol, insulin resistance.

INTRODUCTION

Patients with Obstructive sleep apnea (OSA) presents episodes of obstruction of the upper airway during sleep leading to increase of excessive daytime sleepiness, respiratory, cardiac and metabolic disorders. Approximately 4% of middle-aged men and 2% of middle-aged women have OSA considering an apnea hypopnea index (AHI) ≥ 5 [1]. OSA is associated with cardiovascular risk factors such as hypertension [2], insulin resistance [3], diabetes [4] or dyslipidemia [5]. Patients with OSA are often overweight and obese and they frequently present metabolic abnormalities.

Metabolic syndrome (MS) is a combination of factors, including obesity with central adiposity, glucose intolerance, dyslipidemia and hypertension [6]. Its prevalence tends to increase worldwide due to increase of obesity.

The correlation between OSA and MS is complex and incompletely understood. Indeed, the independent association between OSA and insulin resistance has been evaluated previously [3]. In the Sleep Health Heart Study [2] an association between OSA and cardiovascular risk factors, including some of the components of MS has been described. Also in European and Asian population [7,8] a significant association between OSA and MS has been observed. More recently, a significant relationship was observed between AIH and some MS components in Mediterranean population [9].

Therefore, our first aim was to know the prevalence of MS in a sample of consecutive patients evaluated for suspected sleep disordered breathing. The second aim of the present investigation was to determine which of the MS components were associated with OSA severity.

MATERIAL AND METHODS

This prospective study analyzed 141 adult patients with clinical suspicion of OSA who had been referred for polisomnography to the University Hospital Mutua Terrassa between March 2007 and January 2008. No participant suffered acromegaly, chronic renal failure, chronic autoimmune disease or pregnancy. No patient received steroids or hormonal therapy. There were no differences in

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included patients taking hypoglycemic, hipolipemiant and /or antihypertensive agents. The study was approved by the Ethics Committee of our institution and all patients signed an informed consent.

Clinical measurements were collected in all included patients: medical history, medication use, blood pressure in sitting position (3 measurements), body mass index (kg/m2), neck circumference (at laryngeal prominence) and waist circumference (measured at the last rib and the iliac crest). Daytime sleepiness was measured by the Epworth Sleepiness Scale (ESS). The percentage of body fat was determined using a bioelectrical impedance system (Omron HBF-306). Spirometry (micro 6000 spirometer, Medisoft, Belgium) according to ERS-ATS standards was performed in all included patients [10]. After fasting overnight, venous blood samples were obtained. Glucose, total cholesterol, HDL cholesterol, triglycerides and insulin were measured

Polysomnography

The diagnosis of OSA was performed by standard polysomnography (SleepLab Pro-Viays, USA) recording electroencephalography (C4A1, C3A2, O2A1, O1A2), bilateral electrooculography, submental and bilateral tibialis anterior electromyography, electrocardiography, oxygen saturation, body position, thoracic and abdominal movements, oronasal flow by thermistor, nasal flow by cannula and snoring. The analysis of polysomnogram data was performed manually using the Rechtschaffen and Kales method [11]. Apnea was defined as the absence or reduction of over 90% of the respiratory signal with duration of at least 10 seconds. The hypopnea was defined as an airflow reduction between 30% and 90% with a minimum of 10 seconds accompanied by an oxygen desaturation more than 3% and / or arousals [12]. We defined sleep fragmentation based on the number of awakenings per hour. Oxygen desaturations were measured as the percentage of recording time with oxygen saturation below 90% (T<90). The apnea hypopnea index (AHI) was calculated by dividing the total number of respiratory events by the total number of hours of sleep. Three groups were defined according to the result of AIH: non OSA (AHI <5), mild-moderate OSA (AHI≥ 5 <30), and severe OSA (AHI≥ 30).

Definition of Insulin Resistance

Homeostasis assessment model (HOMA) was used as a measure of insulin sensitivity according to the formula: fasting plasma glucose (mg / dl) x fasting plasma insulin (U / ml) / 22.5 [13]. HOMA index was not calculated in patients with diabetes mellitus type I or type II who received insulin [14].

Definition of Metabolic Syndrome

The occurrence of MS was defined as the presence of 3 or more of the following criteria [15]: waist circumference >102 cm in men or >88 cm in women, fasting glucose ≥ 100 mg / dl or treatment with oral agents, triglycerides ≥ 150 mg / dl or treatment for it, HDL cholesterol <40 mg / dl in men or < 50 mg / dl in women or lipid-lowering treatment, blood pressure ≥ 130/85 mmHg or taking antihypertensive treatment. We defined a metabolic score calculated based on the sum of each of the identified positive criteria (range 0-5) [16].

Statistical Analysis

Data were reported as mean ± SD or median (interquartile range) for parametric and nonparametric variables.The categorical variables were presented as frequency distribution, and were compared using the chi-quare test of Fisher exact test. The comparison between different groups regarding quantitative variables was performed using analysis of variance or Kruskall Wallis test, when appropriate. The correlation between quantitative variables was performed using Spearmen correlation test. We performed multiple regression analysis in order to know the independent predictors of AHI, sleep fragmentation and oxygen desaturations. Independent variables were age, sex body mass index and components of MS. Significance was considered at the 5% level ($p< 0.05$). Statistical analysis was performed using SPSS v. 10.0 (SPSS Inc. Chicago, IL).

RESULTS

We initially evaluated 148 subjects and 7 were excluded for the following reasons: 3 did not give their consent, 2 patients were taking steroids and in 2 cases a blood analysis was not performed. Of the 141 remaining, 104 (73%) were male and 37 (27%) women. The mean age was 54 ± 11 years. According to AHI criteria, 25 (17%) subjects had no OSA, 41 (29%) had mild-moderate OSA, and 75 (53%) had severe OSA. With regard to previous treatment, 53 (37%) patients were taking antihypertensive drugs, 15 (10%) patients were receiving oral antidiabetic agents and 35 (25%) patients were taking hypolipemiant drugs. There were no significant differences in age, sex, tobacco and alcohol consumption, use of antihypertensive, antidiabetic or hypolipemiant drugs between patients with and without OSA Patients with severe OSA had a higher waist circumference ($p <0.002$), greater neck circumference ($p <0.001$) and were more obese ($p <0.001$). In the severe OSA group a significant daytime sleepiness ($p<0.001$), sleep fragmentation ($p<0.001$) and oxygen nocturnal desaturation ($p<0.001$) were also observed. Clinical and polysomnographic characteristics are showed in Table **1**. A significant decrease in HDL cholesterol and increase in glucose and triglycerides levels were observed in severe OSA. In addition, metabolic score and HOMA values increased with the severity of OSA (Table **2**).

The prevalence of MS was higher in OSA patients (43% in mild-moderate group, 81% in sever group) than in non-OSA subjects (32%).

Patients with severe OSA met a higher number of MS components due to higher rate of glucose, triglycerides, HDL cholesterol and blood pressure than patients without OSA (Fig. **1**). However, there were not statistically significant differences between severe OSA and mild-moderate OSA group.

The correlation analysis between AHI, arousals, T<90 and metabolic parameters showed statistical significance, except for some triglycerides values (Table **3**).

In a multiple regression model adjusted by sex, age and BMI, the presence abdominal obesity ($p <0.02$), high glucose ($p <0.01$) and low HDL cholesterol levels ($p <0.001$) were independently associated with AHI. Moreover, low HDL cholesterol ($p <0.01$) was the only variable related to sleep

Table 1. Demograhic Characteristics of the Cohorts of Patients

	Non OSA	Mild-Moderate OSA	Sever OSA	P
Sex (M/F)	14/11	31/10	59/16	n.s.
Tobacco	9 (36%)	18(43%)	34 (45%)	n.s.
Alcohol	6 (24%)	12(29%)	15 (20%)	n.s.
Antihypertensive	9 (36%)	12 (29%)	32 (42%)	n.s.
Antidiabetic	0	5 (12%)	10 (13%)	n.s.
Hypolipemiant	4 (16%)	8 (19%)	23 (30%)	n.s.
Waist (cm)	103.5(SD 8.9)	107 (SD 17.4)	113.4 (SD12.5)	0.002
Neck (cm)	39.3 (SD 3.8)	41.1 (SD 3.7)	43.5(SD 3.8)	0.001
BMI (Kg/m2)	30 (IQR 7.1)	30.4 (IQR 6.5)	34.1 (IQR 7.2)	0.001
SBP (mmHg)	120 (IQR 25)	120 (IQR 30)	130 (IQR 35)	n.s.
DBP (mmHg)	70 (IQR 13.7)	80 (IQR 17.5)	80 (IQR 20)	0.05
% body fat	36.6 (IQR 12)	32.5 (IQR 11.2)	37.5 (IQR 10.5)	n.s.
FEV1 (%)	87 (SD 36.8)	96.8 (SD 23.5)	92.2 (SD 18.4)	n.s.
FVC (%)	95.4 (SD 38)	99.2 (SD 23.08)	93.9 (SD 17.9)	n.s.
Epworth	7.5 (IQR 4.2)	10 (IQR 10.5)	12 (IQR 5.5)	0.001
Arousal index/h	18.5 (IQR 11.2)	31 (IQR 22.5)	66 (IQR 25.5)	0.001
Total sleep time (h)	4.8 (IQR 1.6)	4.9 (IQR 1.05)	4.8 (IQR 1.3)	n.s.
Stage 1 (%)	5 (IQR 4.2)	5 (IQR 4-5)	7 (IQR 6.5)	n.s.
Stage 2 (%)	63.5 (IQR 14.5)	69 (IQR 10.5)	74 (IQR 16)	0.007
Stage 3 (%)	11 (IQR 10.7)	7 (IQR 11)	5 (IQR 9)	0.01
REM (%)	14.5 (IQR 18.7)	17 (IQR 9.5)	13 (IQR 10.5)	0.007
T<90 (%)	2 (IQR 10.5)	13 (IQR 27.5)	65 (IQR 51.5)	0.001

n.s. non significant, SD standard deviation, IQR interquartile range, BMI body mass index, SBP systolic blood pressure, DBP dyastolic blood pressure, FEV1 forced expiratory volume one second, FVC forced vital capacity, T<90 percentatge of recording time with oxygen saturation below 90%.

Table 2. Metabolic Results of the Cohort According to the Severity of the OSAS

	Non OSA	Mild-Moderate OSA	Sever OSA	P
Subjects	25 (17%)	41 (29%)	75 (53%)	
Glucose (mg/dl)	99.5 (IQR 18.5)	100 (IQR 14.5)	111 (IQR 27.5)	0.001
Cholesterol (mg/dl)	216 (IQR 56.2)	195 (IQR 56)	199 (IQR 69.5)	n.s.
HDL Cholesterol (mg/dl)	46.5 (IQR 13.7)	40 (IQR 22.4)	35 (IQR 8.5)	0.001
Triglycerides (mg/dl)	111 (IQR 83)	109 (IQR 57)	135 (IQR 96)	0.04
Metabolic score	2 (IQR 2)	2 (IQR 2)	4 (IQR 1)	0.001
Insulin (µU/ml)	11 (IQR 4.7)	6.7 (IQR 5.9)	13.1 (IQR 9.5)	ns
HOMA	2.8 (IQR 1.5)	1.78 (IQR 1.7)	3.5 (IQR 3.5)	0.001

n.s. non significant, IQR interquartile range, HOMA homeostasis assessment model.

fragmentation. Finally, high glucose ($p< 0.003$) and low HDL cholesterol levels ($p <0.019$) were significantly associated with oxygen desaturation.

DISCUSSION

This present study shows that, in consecutive patients with OSA, MS prevalence is high, especially in severe subjects. The metabolic changes include higher levels of glucose, triglycerides, blood pressure and lower levels of HDL cholesterol. These data were confirmed by other authors [9, 17-20]. Multiple regression analysis controlling for sex, age and BMI confirms an independent association between obstructive events, sleep fragmentation and oxygen desaturation with some components of MS. Our results

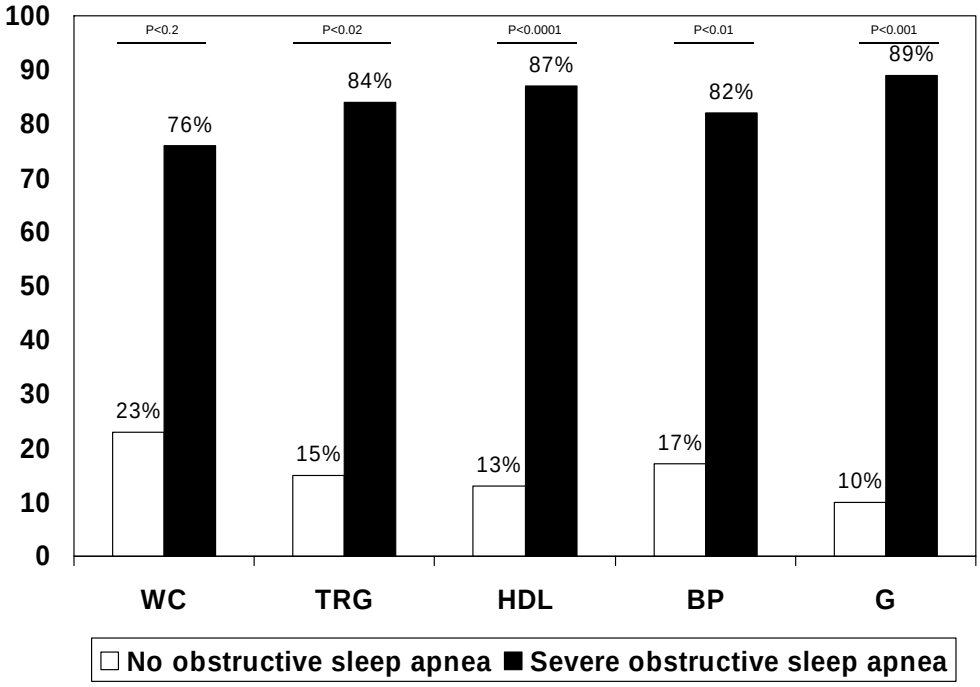

Fig. (1). MS components in severe obstructive sleep apnea (OSA) and non-OSA. Abbreviations: WC, waist circumference; TRG, triglycerids; HDL, high density lipoprotein cholesterol; BP, blood pressure; G, glucose.

Table 3. The Correlation Analysis Between AHI, Arousals, T<90 and Metabolic Parameters

	AHI r	**Arousals r**	**T<90 r**
BMI	0.445 (p<0.001)	0,396 (p<0.001)	0.48 (p<0.001)
Waist circumference	0.43 (p<0.001)	0.32 (p<0.001)	0.41 (p<0.01)
SBP	0.21 (p<0.01)	0.24 (p<0.03)	0.22 (0.007)
DBP	0.22 (p<0.006)	0.21 (p<0.01)	0.12 (n.s)
Glucose	0.39 (p<0.001)	0.355 (p<0.001)	0.38 (p<0.001)
HDL cholesterol	0.32 (p<0.001)	0.22 (p<0.01)	0.11 (0.02)
Triglycerides	0.18 (p<0.03)	0.15 (n.s.)	0.09 (n.s)

n.s. non significant, BMI body mass index, SBP systolic blood pressure.
DBP diastolic blood pressure, AHI apnea-hypoapnea index, T<90 percentatge of recording time with oxygen saturation below 90%.

suggest that OSA has effect on metabolic risk factors, which are components of MS.

The prevalence of MS in OSA patients according to the NCEP ATP III ranges between 23-87% [7,16]. Recently, in a large series of Mediterranean OSA patients the prevalence of MS was between 51.2%-69.8% [9,21]. Also, the number of components of MS increases with OSA severity in the same population [9]. Our results are similar in mild-moderate OSA, but the prevalence rate of MS was higher in severe OSA, probably due to higher BMI and higher neck circumference. The same prevalence was observed in severe OSA patients in Greece [21], also with the same BMI and neck circumference. In morbid obese Spanish patients with OSA included in a bariatric surgery program the prevalence of MS was 70% [22], lower than described in our population. Probably, it is plausible to consider that metabolic dysfunction could be associated not only with BMI but also with OSA severity.

In our study we found a significant correlation between OSA severity and abdominal circumference, but not with body fat measured by bioimpedance. These results were confirmed by other authors after adjusting for confounding factors [9,18,23]. It is known that both abdominal circumference and body fat are associated with increased visceral fat determined by CT scan [24]. There are results that show a significant association between visceral obesity and the severity of OSA [25]. Visceral fat is a common feature observed in MS and OSA, and is a risk factor for cardiovascular events, insulin resistance and diabetes mellitus [23].

Insulin resistance was assessed using the HOMA score. MS is considered the clinical manifestation of insulin resistance, although the relationship between two entities is not clear. The present study showed that HOMA values increased significantly with OSA severity. Similar results have been described by Bonsignore [9], although such

relationship disappeared after adjustment for BMI. McArdle and colleagues [19] found an increased insulin resistance in patients with OSA compared with matched controls. Also, relationship was found between insulin resistance and indices of OSA severity (AHI, oxygen desaturation). Other studies however showed that OSA may be associated with MS but not with insulin resistance [26], probably due to a high number of components in severe OSA.

Several lines of evidence support an independent association between OSA and dysregulation of lipid metabolism. Results of the Sleep Heart Health Study showed a correlation between respiratory events and lipid profile abnormalities [27]. In both community-based [6] and hospital [28,29] populations severe OSA is associated with low HDL cholesterol levels independent of confusing factors as obesity. Also, an independent association between AHI and low levels of HDL cholesterol was observed in morbid obese patients with OSA [22]. We found a significant association between AHI, sleep fragmentation and nocturnal oxygen desaturation with low levels of HDL cholesterol, suggesting that these factors may be involved in the pathogenesis of lipid abnormalities. A sleep fragmentation is related with high levels of total cholesterol and low levels of HDL cholesterol [30,31]. Although the ultimate relationship between OSA and alterations in lipid metabolism remains to be defined, it is known that patients with OSA have an increase of sympathetic activity and nocturnal hypoxemia [32]. Intermittent hypoxia in animal models is involved in the pathogenesis of abnormal lipid profile, modifying the expression of lipoprotein lipase, which is key in the HDL cholesterol synthesis [33].

Diabetic patients often are obese and have a high prevalence of OSA [34]. Clinical studies have shown an increase in serum glucose in patients with OSA independent of obesity [3,35]. In the present study we observed an independently association between high glucose levels, AHI and oxygen desaturation. However, in the Wisconsin cohort study [27] this association had not been demonstrated. Furthermore, the effect of CPAP treatment on glucose levels is variable, and improving insulin resistance in non-obese patients in a short term has also been documented [36]. Although positive effect has been shown in observational studies, randomized controlled studies [37] have shown no changes in insulin resistance after treatment with CPAP. Although diabetes is correlated with visceral and abdominal obesity, glucose abnormalities have also been documented in non-obese patients with OSA [20,38].

Differences with previous studies may be explained by different reasons. First, our study population includes patients with suspected OSA and with a high prevalence of hypertension, also visible in the control group. Second, our series includes patients treated with antihypertensive, antidiabetic and hypolipemiant drugs, which could not be discontinued for ethical reasons. We think that this population is more representative of patients studied in our sleep units. It is possible that OSA itself may modify any of the components of MS, or that both processes have common risk factors.

Our study has some limitations. First it is a cross-sectional study, and does not prove cause-effect relationships between OSA and metabolic abnormalities, data referred by other authors [39]. Second, participants were recruited from subjects attended our sleep unit and were not matched for BMI, waist circumference or body fat percentage. However, similar results have been observed in non-obese OSA patients (20). Therefore, it's difficult to know if OSA itself can produce or aggravate metabolic abnormalities. For this reason our results may not be applicable to general population. Third, the study comprised a relatively small number of participants in all groups, and therefore could affect the results.

In conclusion, our finding suggests that prevalence of MS in patients with OSA is high and increases according to the severity of OSA. We find a significant association between the presence of OSA and MS. In OSA patients is important to assess the presence of MS or its components, and that early intervention could reduce morbidity and mortality.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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