

Study of dyslipidemia in patients with Obstructive Sleep Apnea Syndrome in primary health care

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Summary Background. Obstructive Sleep Apnea Syndrome (OSAS) is associated with several morbidities. The most important ones are obesity, hypertension and diabetes mellitus. A clear relationship of OSAS and dyslipidemia is yet to be demonstrated.

Objectives. To evaluate the prevalence of dyslipidemia as a morbidity associated with OSAS and to understand its relationship with the severity of OSAS.

Material and methods. We randomly selected 92 patients diagnosed until the end of May 2016 with OSAS from two primary health care units and 184 patients as controls (no OSAS diagnosed) from random lists of patients matched in age and gender with patients with OSAS.

We calculated the prevalence of the classified comorbidities (overweight, hypertension, type 2 diabetes mellitus and dyslipidemia) in both groups. We used logistic regression to check the association between them. We evaluated the relationship between dyslipidemia and OSAS severity by using the Apnea/Hypopnea Index (AHI).

Results. The prevalence of dyslipidemia was 80% in patients with OSAS. Patients with OSAS were diagnosed as overweight (97%), had arterial hypertension (89%) and type 2 diabetes mellitus (43%). OSAS was not independently related to type 2 diabetes mellitus ($p = 0.101$) and to dyslipidemia ($p = 0.389$). However, overweight and arterial hypertension were related independently to OSAS ($p < 0.001$) with a risk for OSAS. The prevalence of dyslipidemia in patients with mild, moderate and severe OSAS was 22%, 13% and 25%, respectively.

Conclusions. Patients with OSAS have a high prevalence of dyslipidemia despite not being independently related. There were no statistical differences between patients with mild, moderate and severe OSAS.

Key words: sleep apnea syndromes, dyslipidemias, overweight, hypertension, diabetes mellitus type 2.

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Background

Obstructive Sleep Apnea Syndrome (OSAS) is the most common sleep disorder [1], and it is a significant source of morbidity and mortality [1–5]. It can be defined by transitory episodes of apnea, and it is characterized by the presence of sleep fragmentation and excessive daytime sleepiness associated with cardiovascular and neurocognitive disorders [6]. This syndrome relates to a state of chronic hypoxia caused by recurrent episodes of temporary total or partial obstruction of the upper airways during sleep [2, 6]. OSAS affects around 4% of middle-aged men and 2% of middle-aged women in developed countries [2, 6]. In Portugal, the prevalence of OSAS is estimated, in the population of 25 years of age or more, to be around 0.89% [5]. It generally affects middle-aged, obese male individuals [5]. Several studies recognize OSAS as an independent risk factor for cardiovascular diseases [2, 6, 7].

Dyslipidemia is one of the risk factors for atherosclerosis [8]. It is defined by an elevation of total cholesterol (≥ 190 mg/dl), a reduction of HDL (≤ 40 mg/dl in men and ≤ 45 in women), an

elevation of LDL (≥ 115 mg/dl) and triglycerides (≥ 150 mg/dl) [8]. The Portuguese prevalence of hypercholesterolemia is 47%, and an elevation of LDL occurs in 38% [9]. Hypertriglyceridemia is less prevalent, affecting about 13% of the population [9].

Several comorbidities have been associated with OSAS, among them, cardiovascular complications [10]. In Portugal, the most frequent cardiovascular risk factors in patients with OSAS are arterial hypertension (75.9%), obesity (74.2%) and diabetes mellitus (34.1%) [5].

Dyslipidemia has been studied as a comorbidity related to OSAS, but studies of such association are scarce, and clinical evidence is limited [7, 11, 12]. Some studies have shown evidence of an existing relationship between the elevation of the prevalence of dyslipidemia and OSAS, but a clear association has not yet been found [2, 4, 10–15]. Dyslipidemia and OSAS severity could be related, higher levels of dyslipidemia being associated with increased Apnea/Hypopnea Index (AHI) [2]. As such, reinforcing cardiovascular prevention of dyslipidemia and acting therapeutically could be important in improving cardio-vascular health associated with OSAS [5].



Objectives

The aim of this study was to evaluate the prevalence of dyslipidemia as a comorbidity associated with OSAS and to understand its relationship with the severity of OSAS and its complications.

Material and methods

This was an observational cross-sectional study involving a target population of patients with Obstructive Sleep Apnea Syndrome (OSAS) followed in a General Practice and Family Medicine setting from two Primary Care Units in Central Portugal in 2016.

As exclusion criteria: patients with the P06 International Classification for Primary Care2 (ICPC2) code who were not treated using continuous positive airway pressure (CPAP) and patients with other types of sleep disturbance (insomnia, hypersomnia, nightmares and sleepwalking). Data was gathered from randomly selected e.processes from the patient lists of both health units using the mim@uf program until obtaining the needed sample. In the second stage, the same data was collected for controls (without OSAS) using random lists paired in age and gender with the cases of OSAS.

A questionnaire with the variables under study was used, including:

- gender,
- age (years),
- Body Mass Index (BMI) in kg/m² registered in the process,
- dyslipidemia/lipids metabolism coded on the list of problems (T93),
- Arterial Hypertension (HTA) coded in the list of problems (K86),
- type 2 Diabetes Mellitus (DM) coded in the list of problems (T90),
- total cholesterol, LDL, HDL and triglycerides values,
- Apnea/Hypopnea Index (AHI) registered in the process (only for the cases),
- anti-dyslipidemia drugs prescribed during the last 6 months,
- questionnaire with the variables under study:
 - Mild OSA: IAH = 5.0–15.0/h,
 - Moderate OSA: IAH = 15.1–30.0/h,
 - Severe OSA: IAH > 30.0/h.

Data was collected from October to December 2016 after its approval by the Ethics Commission of ARS Center and authorizations from the Health Units.

Qualitative measures were described using absolute and relative frequencies, and the quantitative measures were described by their average and standard deviation when normally distributed.

Student's *t*-test was used for independent numeric variables in the groups with and without OSAS. A bivariate analysis was performed between OSAS and each of the associated comorbidities (overweight, arterial hypertension and diabetes mellitus) and between dyslipidemia and AHI.

A multivariate analysis by logistic regression was performed to evaluate the independent relationship between each of the comorbidities and OSAS, determining the respective relative risks. Any value of *p* < 0.05 was considered statistically significant.

Results

The sample of 92 OSAS cases and 184 controls used in this study was mostly made up of male individuals (74%) aged between 35 and 89. The average age was 63.763.7 ± 10.3 years (Table 1). No significant statistical differences were found between the group of patients with OSAS and the group without OSAS for gender and age.

Table 1. Sample demographic characterization

Parameters	Cases (n = 92)	Controls (n = 184)	p
Gender (M:F)	68 (74%):24 (26%)	136 (74%):48 (26%)	1
Average age	63.7 ± 10.3	63.7 ± 10.3	1
Minimum age	35	35	1
Maximum age	89	89	1

The data is presented by absolute frequency and proportion or average and standard deviation. Chi-squared and Student's *t*-test tests were used for independent samples.

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In a bivariate analysis, significant statistical differences were observed in all comorbidities between the group of patients with OSAS and without OSAS. The most frequent comorbidities in patients with OSAS were overweight (97%), arterial hypertension (89%) and dyslipidemia (80%). Type 2 diabetes mellitus was found in 43% of the patients (Table 2).

Table 2. Association of comorbidities of patients from the study with OSAS

Parameters	OSAS (n = 92)	Controls (n = 184)	p
Overweight	89 (97%)	148 (81%)	< 0.001
Arterial hypertension	82 (89%)	125 (68%)	< 0.001
Dyslipidemia	74 (80%)	110 (60%)	< 0.001
Type 2 diabetes mellitus	39 (43%)	42 (23%)	< 0.001

The data is presented by absolute frequency and proportion. The chi-squared test was used.

A multivariate analysis to study the relationship of OSAS with each of the associated comorbidities (overweight, HTA, type 2 diabetes mellitus and dyslipidemia) was carried out. OSAS was not independently related to diabetes mellitus type 2 (*p* = 0.101) and to dyslipidemia (*p* = 0.389). However, overweight and arterial hypertension were independently related with OSAS, with a relative risk of having OSAS of 5.51 and of 2.73, respectively.

Table 3. Multivariate analysis by logistic regression of associated comorbidities independently of OSA

Parameters	p	RR	CI 95% inferior	Superior
Overweight	0.007	5.51	1.6	19.02
Arterial hypertension	0.014	2.73	1.2	6.1

Patients with OSAS were more often on medical treatment for dyslipidemia (92%) when compared to controls (84%, *p* ≤ 0.001).

According to AHI, patients were distributed by severity (Table 4).

Table 4. OSAS case distribution according to severity

Apnea/Hypopnea Index	Cases (%)
< 5	16 (27%)
Mild (≥ 5 and < 15)	16 (27%)
Moderate (≥ 15 and < 30)	12 (19%)
Severe (≥ 30)	16 (27%)

AHI < 5; mild: ≥ 5 and < 15; moderate: ≥ 15 and < 30; severe: ≥ 30. The data is presented by absolute and standard deviation frequency. *n* = 60.

Table 5 shows the prevalence of dyslipidemia, distributed by the severity of OSAS, estimated by AHI. No statistically significant differences were observed in the presence of dyslipidemia among the patients with different levels of severity using the chi-squared test. The prevalence of dyslipidemia was lower in patients with moderate OSAS (13%) compared to patients with AHI < 5 (20%) and mild OSAS (22%).

Parameters/ /AHI	< 5	Mild	Moderate	Severe	<i>p</i>
Dyslipidemia	20%	22%	13%	25%	0.322

Absence of OSA: < 5; OSA presence: > 5: mild: ≥ 5 and < 15; moderate: ≥ 15 and < 30; severe: ≥ 30 . The data is presented by absolute frequency in percentage. *n* = 60. The chi-squared test was used.

Discussion

As was reported in other studies, we found that overweight, arterial hypertension and diabetes mellitus type 2 were associated with OSAS [5, 6, 10, 17]. Overall, these values were higher than those described in other studies [5, 6, 10, 17]. Such a fact might be explained by the reduced size of the sample and possible bias in the selection of patients from only two health units used in the sample collection.

It has been shown that overweight plays an important role in the development of OSAS [5, 14]. In this sample with OSAS, 97% were overweight, a higher prevalence than previously [14]. The prevalence of overweight was significantly more frequent in patients with OSAS. It is described that 40% of patients with OSAS have arterial hypertension, but this value could be higher if we consider the fact that some patients with arterial hypertension are thought to have hidden OSAS [14]. A type 2 diabetes mellitus prevalence of 43% was found, significantly higher in patients with OSAS. OSAS can be involved in the pathogenesis of glucose metabolism alteration [14].

The prevalence of dyslipidemia in OSAS patients in this study is higher than the values found in patients without OSAS, with significant statistical differences in bivariate analysis. For this association, studies are scarce, and evidence is limited [7, 12]. Some studies show a relationship between dyslipidemia and the prevalence of OSAS [2, 4, 10–15, 18], although a clear association has not yet been shown [2, 4, 12, 13, 15].

A multivariate analysis was carried out in order to exclude confounding variables. A significant independent relationship was found between OSAS and overweight (OSAS risk 5.51 times higher) and between OSAS and arterial hypertension (OSAS risk 2.73 times higher).

As for type 2 diabetes mellitus, its relation to OSAS was not independent from the other factors, although the prevalence of type 2 diabetes mellitus was higher in patients with OSAS. This was reversed when the confounding factors were adjusted, as was seen in other studies [10].

In the multivariate analysis, there was no significant and independent association between dyslipidemia and OSAS, which

might reinforce the hypothesis of OSAS not being independently related to dyslipidemia. However, its presence in these patients might be better explained by an association with other present comorbidities (overweight, arterial hypertension and diabetes mellitus type 2). The state of insulin resistance is a mechanism that might be present in the development of the previous comorbidities, particularly in the origin of metabolic syndrome [19–22]. Some studies even suggest OSAS as being one of the components of metabolic syndrome [10], classifying it as syndrome Z [10, 14, 19, 23]. Thus, the dyslipidemia which occurs in a patient with OSAS can be related to the metabolic alterations that lead to the development of atherosclerosis, worsening cardiovascular outcomes [21]. The fact that treatment with CPAP has shown a mild improvement in metabolic changes [12, 18, 24–27] might explain the fact that these may not be directly associated to OSAS. Other studies state that night chronic hypoxemic state, present in OSAS, is independently related with dyslipidemia [4] in spite of limited evidence [15].

Previous studies have shown that dyslipidemia might be related to the severity of OSAS [2, 7]. In this study, this possible relationship was evaluated using AHI. No statistical differences were observed between the prevalence of dyslipidemia and the different degrees of severity of OSAS (< 5, light, moderate and severe). The prevalence of dyslipidemia in OSAS patients with AHI < 5 was 20%, in mild OSAS – 22%, and in severe OSAS – 25%, meaning that the prevalence might increase with the severity of OSAS. However, in the case of moderate OSAS, the prevalence of dyslipidemia was only 13%. These results were also found in other studies [2]. This might be explained by the reduced sample size, by the high levels of omissions of registration of the AHI parameter and by the fact that there was a small number of patients with moderate OSAS. As mentioned before, as well as in other studies, the confounding factors (overweight, arterial hypertension and diabetes mellitus) may represent a determining role in the lipid profile of patients and in the different stages of OSAS severity [2, 7].

As for limitations of this study, one must bear in mind the reduced size of the sample, even though it was calculated to be representative of the population. We studied a mostly male sample, which is in accordance with previous studies [2, 5, 6]. The average age was 63.7 ± 10.0 years, an older age than most other studies described [2, 5, 6]. This fact might be explained by underdiagnosed OSAS in Portugal or be the consequence of a late diagnosis [5].

Another limitation could be the fact that the information recorded in the electronic clinical processes might not be correct or was missing, namely for the Apnea/Hypopnea Index (IAH). Future studies will be needed to better explain this relationship in larger samples and while excluding possible confounding factors.

Conclusions

In our sample, patients with OSAS had a higher prevalence of dyslipidemia which was not independent from other cardiovascular risk factors. Dyslipidemia might be better explained in OSAS patients in a context of associated overweight and cardiovascular risk. Dyslipidemia and OSAS severity were not statistically associated.

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