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Original Article

Long Term Effect of Autoadjusting Positive Airway Pressure on C-Reactive Protein and Interleukin-6 in Men With Obstructive Sleep Apnoea Syndrome

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ABSTRACT

Background and objectives: Obstructive sleep apnoea (OSA) has been increasingly linked to cardiovascular disease. Inflammatory processes associated with OSA may contribute to this morbidity. Some studies have reported serum levels of high sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) to be increased in these patients. Primary objective: investigate the impact of short and long-term autoadjusting positive airway pressure (APAP) therapy on IL-6 and hs-CRP serum levels in patients with moderate to severe obstructive sleep apnoea. Secundary Objective: evaluate the basal hs-CRP and IL-6 levels in OSA patients and its possible relation to OSA severity, independently of confounders and compare the hs-CRP levels in OSA patients with those in community controls.

Patients and methods: This is a prospective study including 98 male patients with moderate to severe OSA confirmed by domiciliary sleep study. Malignancy and chronic inflammatory diseases were exclusion criteria. hs-CRP and IL-6 serum levels were evaluated before APAP, 9 days and 6 months after therapy. Community controls (n=103) were selected using random digit dialling, and matched by age and body mass index (BMI) for comparison of hs-CRP levels at baseline.

Results: The studied population had a mean age of 55.3±10.7 years, mean BMI 33.2±5.0kg/m^2, mean apnoea-hypopnoea index 51.7±21.3/h and mean desaturation index 86.3±5.3/h. The APAP compliance was good: 91.27&%×000B1;20.45 days usage and 5.76±1.59h/night of usage.

Mean basal hs-CRP and IL-6 serum values were 0.52±0.53 μg/l and 17.7±22.5 μg/l, respectively. CRP levels at baseline correlated significantly with apnoea-hypopnoea index, desaturation index and minimum nocturnal oxygen saturation. IL-6 levels at baseline correlated significantly and negatively with minimum nocturnal oxygen saturation. When adjusting for confounding factors found in this study, all these relations lost significance.

CRP is significantly increased in patients when compared to controls (*P*=.002) and when considering hs-CRP cardiovascular risk stratified categories, cases had significantly more patients at high risk of cardiovascular events than controls (*P*=.002).

After adjustment for BMI and arterial hypertension, cases had an almost twofold moderate risk of cardiovascular events and more than a twofold severe risk of cardiovascular events when compared to controls.

We found no significant difference between hs-CRP and IL-6 concentrations pre-treatment and in two moments post-treatment (9 days and 6 months) (CRP: *P*=.720 and *P*=.387, respectively; IL-6: *P*=.266 and *P*=.238, respectively).

Conclusions: OSA is associated with a low-grade inflammatory process; hs-CRP serum levels are elevated in OSA patients when comparing to community controls, independently of age and BMI and the former have a significantly higher risk of cardiovascular events when compared to the latter. There was no significant decrease of both inflamatory mediators (hs-CRP, IL-6) after short and long-term APAP therapy.

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Efecto a largo plazo de la presión positiva automática en la vía aérea sobre la proteína C reactiva y la interleucina-6 en varones con síndrome de apnea obstructiva del sueño

Palabras clave:
Proteína C reactiva de alta sensibilidad
Interleucina-6
Apnea obstructiva del sueño

RESUMEN

Introducción: La apnea obstructiva del sueño (AOS) se ha vinculado de forma creciente con las enfermedades cardiovasculares. Los procesos inflamatorios asociados a la AOS pueden contribuir a esta morbilidad. Algunos estudios han señalado que las concentraciones séricas de proteína C reactiva de alta sensibilidad (PCR-as) y de interleucina-6 (IL-6) están aumentadas en estos pacientes. El objetivo principal del estudio has sido investigar la repercusión a corto y largo plazo del tratamiento de presión positiva automática en la vía aérea (APAP) sobre las concentraciones séricas de PCR-as e IL-6 en pacientes con AOS clasificada entre moderada y grave. Como objetivo secundario, nos propusimos evaluar las concentraciones basales de PCR-as e IL-6 en los pacientes con AOS y su posible relación con la gravedad de dicho síndrome, independientemente de los factores de confusión, y comparar las concentraciones de PCR-as en los afectados de AOS con los de una población de control procedente de la comunidad.

Pacientes y métodos: Se trata de un estudio prospectivo que ha incluido a 98 pacientes varones con AOS de moderada a grave, confirmada mediante un estudio domiciliario del sueño. Las neoplasias malignas y las enfermedades inflamatorias crónicas fueron criterios de exclusión. Se evaluaron las concentraciones séricas de PCR-as y de IL-6 antes de la APAP, a los 9 días y a los 6 meses del tratamiento. Los controles de la comunidad (n=103), que se seleccionaron mediante llamadas telefónicas aleatorias, se emparejaron por edad e índice de masa corporal (IMC) con el grupo de pacientes con objeto de comparar las concentraciones de PCR-as al inicio del estudio.

Resultados: La población estudiada presentaba una media (± desviación estándar) de edad de 55,3±10,7 años, un IMC medio de 33,2±5,0kg/m^2, un índice medio de apneas-hipopneas de 51,7±21,3/h y un índice de desaturación de 86,3±5,3/h. El cumplimiento del tratamiento con APAP fue bueno, con un uso de un 91,27±20,45% de los días y de 5,76±1,59h/noche.

Al inicio del estudio, los valores séricos medios de PCR-as e IL-6 fueron de 0,52±0,53 y 17,7±22,5 μg/l, respectivamente. Los de PCR-as se correlacionaban de forma significativa con el índice de apneas-hipopneas, el índice de desaturación y la saturación de oxígeno mínima durante la noche, y los de IL-6 estaban correlacionados de forma significativa y negativa con la saturación de oxígeno mínima durante la noche. Al ajustar por los factores de confusión encontrados en el estudio, todas estas relaciones perdieron significación.

La PCR-as se encontraba significativamente elevada en los pacientes respecto a los controles (*P*=.002). Al considerar las categorías de estratificación del riesgo cardiovascular mediante la PCR-as, en el grupo de pacientes era significativamente mayor el número de personas con riesgo elevado de episodios cardiovasculares en comparación con el grupo control (*P*=.002).

Tras el ajuste por IMC e hipertensión arterial, el grupo de pacientes presentaba un riesgo moderado casi 2 veces superior y un riesgo importante más de 2 veces superior de desarrollar episodios cardiovasculares en comparación con el grupo de control.

No encontramos diferencias significativas entre las concentraciones de PCR-as e IL-6 antes del tratamiento y en los 2 períodos posteriores, es decir, a los 9 días y a los 6 meses (PCR: *P*=.720 y *P*=.387; IL-6: *P*=.266 y *P*=.238, respectivamente).

Conclusiones: La AOS está asociada con un proceso inflamatorio de bajo grado. Las concentraciones séricas de PCR-as se encuentran elevadas en los pacientes con AOS al compararlas con las de un grupo de control procedente de la comunidad, independientemente de la edad y del IMC. Además, el grupo de pacientes presentaba un riesgo significativamente mayor de desarrollar episodios cardiovasculares que el de control. No se observó una disminución significativa de las concentraciones de los mediadores inflamatorios (PCR-as e IL-6) tras el tratamiento de APAP a corto ni a largo plazo.

Introduction

Obstructive Sleep Apnoea (OSA) is a common disorder with a prevalence of 2% to 4% in middle-aged adults.[1] It has been increasingly linked to cardiovascular disease.[2,3,4]

Mechanisms such as increased sympathetic activity[5] and endothelial dysfunction have been implicated. Inflammatory processes[6] associated with OSA may also act as potential mediators of cardiovascular (CV) morbidity and mortality in these patients.

Several studies have demonstrated elevated serum levels of Interleukin-6 (IL-6)[7,8,9] and C- reactive protein (CRP)[9,10,11] in OSA patients while others have not.[12,13]

IL-6 is a circulating cytokine known to be secreted from a number of different cells including activated macrophages and lymphocytes.[14] Inflammation is the main stimulus for IL-6 production, but other stimuli also exists, as cigarette smoke[14] and adiposity.[15]

The hepatic synthesis of C-reactive protein (CRP) is largely under the regulation of the pro-inflammatory cytokine IL-6,[16,17] that is believed to represent the major regulator of the hepatic acute phase response.[16,17]

CRP is an important serum inflammation marker that is quite stable across 24h,[18] unlike cytokines, and may reflect the inflammatory response level.

Epidemiological studies show that an elevated CRP level in apparently healthy men and women is a strong predictor of cardiovascular risk[19,20] and some authors have demonstrated that CRP is an independent CV risk factor.[21,22]

CRP may play a direct role in initiation and progression of atherosclerosis.[23] Its proinflammatory and proatherogenic properties have been found in endothelial cells,[24] vascular smooth muscle cells[25] and monocyte-macrophages[26] and CRP levels are also associated with oxidative stress.[27]

Hypoxemia results in increases in IL-6 and CRP[28] in normal humans. Sleep fragmentation and deprivation[6] also induces an increase in cytokines that may underlie inflammatory responses which lead to cardiovascular morbidity.[29]

Continuous positive airway pressure (CPAP) is the primary treatment for OSA.[30,31] Accumulated evidence supports that CPAP also reduces cardiovascular diseases[32,33] and CV risk factors.[34]

Auto-adjusting positive airway pressure (APAP) devices are a recent alternative treatment to traditional CPAP and are able to improve symptoms[35] while increasing long-term treatment compliance[36] without the high costs of CPAP titration.[37] However, different from CPAP, the impact of APAP therapy on cardiovascular and metabolic outcomes in OSA patients is poorly known.[38]

The present study was conducted to primarily evaluate the impact of short and long-term APAP therapy on IL-6 and CRP serum levels in patients with moderate to severe obstructive sleep apnoea and secondarily to evaluate the basal h-CRP and IL-6 levels in OSA patients and its possible relation to OSA severity, independently of confounders and compare the h-CRP levels in OSA patients with those in community controls.

Materials and Methods

Study Design

This study was designed as a prospective study and also a controlled one, at baseline, regarding to h-CRP data.

Subjects

One hundred and two male patients referred for suspected sleep disordered breathing to our Pulmonology- Sleep Disordered Breathing Department were included in the study.

Inclusion criteria were previously stablished: moderate/ severe OSA with criteria for active treatment with nocturnal ventilatory support (AHI>20/h), normal pulmonary function tests (FEV_1/ FVC>70; FEV_1 e FVC>80% predicted) and male gender; as also exclusion criteria: neoplastic diseases, systemic inflammatory chronic diseases, active infectious diseases and systemic long term corticotherapy.

Body Mass Index (BMI) was calculated by the formula weight / height.[2]

Patients received APAP therapy by REM STAR™ Auto (Respironics-Inc., Murraysville USA) device with pre-determined minimum and maximum pressure of 4 and 15 cmH_2O, respectively.

All but four patients concluded the study (n=98). Those who failed to conclude the protocol refered nocturnal APAP intolerance as the reason to quit.

CV risk categories based on h-CRP were previously stablished: low CV risk- h-CRP<1 mg/L; moderate CV risk- h-CRP between 1 and 3 mg/L and severe h-CV risk- h-CRP>3 mg/L.

A representative sample of the adult Porto population assembled as part of an ongoing health and nutrition survey was used as source of controls. A detailed description of the general selection procedures and subject characteristics was made previously.[39]

In brief, subjects were recruited by random digit dialling using households as the sampling frame followed by simple random sampling to select one eligible person among permanent residents in each household that was invited to visit our department for interview and blood collection.

Twenty-five hundred community controls aged 18 to 93 were evaluated corresponding to a participation proportion of 70%. Subjects aged above 64 years scoring less than 24 in the Mini-Mental State Examination[40] were not eligible.

We have selected 103 of these community controls, matched by sex, age and BMI (Body Mass Index) to our patients group, for a comparison of C-reactive protein at baseline.

The local institutional ethics committee approved the study that was performed in accordance with the guidelines of the Declaration of Helsinki and its current revision and all participants gave written informed consent.

Study Procedures

Sleep Study

An overnight sleep study was performed using a five-channel recording device (*Alphascreen; Vyasis*) which has been validated previously.[41] This device produces a computorized recording of variations in oronasal airflow (measured by nasal cannula), body position, wrist actimetry, pulse rate and arterial oxygen saturation (measured by finger pulse oximetry). The device estimates the total sleep time from the wrist actimetry registry, eliminating those periods with high activity. It automatically calculates the number of apnoeas plus hypopnoeas per hour of estimated sleep time (automatic respiratory disturbance index) and it also provides information of desaturations>4% per hour of estimated sleep time and the cumulative percentages of sleep time under 90% oxygen saturation. In all cases, sleep technicians carried out a manual analysis of the recordings, by counting apnoea (episodes≤20% of previous airflow with at least 10 seconds of duration) and hypopnoea episodes (episodes showing 20 to 50% of the previous airflow, with at least 10 seconds of duration joined with a 4% dip in oxygen saturation), dividing the total number of these episodes by the sleep time in hours, thus obtaining the manual respiratory disturbance index according to established criteria.[42]

Blood Analysis

Fasting morning venous blood samples were collected between 8-10 a.m. in three moments; before treatment, nine days and 6 months after.

Blood samples were immediately sent to the laboratory for estimation of glucose, lipids and high sensitivity CRP (h-CRP) while a specimen of clotted blood was centrifuged at 4000g for 20 min for serum, which was stored at –26°C in eppendorfs® until IL-6 analysis was performed.

Serum IL-6 concentrations were measured in duplicates with a highly sensitive immunoradiometric assay kit (IL-6-EASIA-CE KAP1261 Biosource® Europe S.A.). The sensitivity of this assay was 0,5 ng/mL, the specificity was 100% and the interassay coefficient of variation was 4,6%.

Statistical Analysis

Data were analyzed using SPSS, release 14.0, and described as mean values and their respective standard deviation for normally, or as median values and corresponding 25th and 75th centiles for clearly non-normally distributed variables. Counts and proportions are reported for categorical variables. Proportions were compared using Chi-square test or *Fisher's* exact test whenever appropriate.

Spearman correlations coefficients were computed to estimate the association between CRP and Il-6 serum levels and participants characteristics at baseline.

For comparison between median values at the three moments studied the non parametric Wilcoxon test for paired samples was used.

In the case-control analysis, cases and controls were matched according to age and BMI. Unconditional logistic regression was used to compute odds ratios (OR) and their respective 95% confidence intervals (95% CI). As BMI persisted higher in cases than in controls (33.4% vs 29.7%; *P*<.001), the final model was adjusted for BMI and also to AH.

Results

The studied population (n=98) and the control group (n=103) presented characteristics that are addressed in table 1, including distribution according to Bray's obesity categories.[43]

Sleep characteristics of study group are depicted in table 2.

During the 6 months of the study, the patients compliance with APAP was good (table 3), pressure on 90% night-time decreased significantly during the study (mean baseline p90=10.8 cmH_2O; mean final p90=10.1; *P*<.001) and the residual Apnoea/ Hypopnoea Index (AHI) reflects the therapy efficacy (mean residual AHI=2.7/h±1.7).

During the study patients did not loose significant weight (mean baseline weight=94.4 kg; mean final weight=94.1 kg; *P*=.545) nor changed their fat distribution (*P*=.151).

Habits and Comorbidities

Data is depicted in table 4.

Table 1
Characteristics of study group and control group

	Study group	Control group
Age (years)	55.3 (SD 10.7)	55.9 (SD 10.8)
BMI[1] (kg/m^2)	33.2 (SD 5.0)	29.7 (SD 3.7)
BMI Class 0 (BMI: 20-25)	4 (3.8%)	8 (7.8%)
BMI Class I (BMI: 25-30)	25 (23.6%)	49 (48%)
BMI Class II (BMI: 30-35)	39 (36.8%)	36 (35.3%)
BMI Class III (BMI: 35-40)	32 (30.2%)	6 (5.6%)
BMI Class IV (BMI>40)	6 (6.7%)	2 (2.0%)
Waist-to-hip ratio	1 (0.1)	0.99 (0.07)
CRP[2]<1.00 mg/L	13 (12.7%)	31 (30.4%)
CRP[2] 1.00-3.00 mg/L	33 (32.4%)	36 (35.5%)
CRP[2]>3.00 mg/L	56 (54.9%)	35 (34.3%)

BMI: body mass index; CDP: C-reactive protein.

Table 2
Sleep characteristics of study group

AHI	51.7 (21.3)
Desaturation index	86.3 (5.3)
Lowest O_2 saturation (%)	70.8 (9.7)
Mean O_2 saturation (%)	86.3 (5.3)

Table 3
APAP compliance

% APAP days of usage	91.27±20.45
Total APAP days of usage	171.2±44.9
Hours per night of APAP usage	5.76±1.59

Table 4
Habits and comorbidities

Habits and comorbidities	Cases, n (%)	Controls, n (%)
Smokers	19 (17.9)	29 (28.4%)
Non-smokers	45 (42.5)	30 (29.4)
Former smokers[a]	42 (39.6)	43 (42.2)
Arterial hypertension	50 (47.2)	32 (31.4)
Congestive heart failure	10 (9.4)	
Stroke	16 (15.1)	3 (2.9)
Acute myocardial infarction	8 (7.5)	4 (3.9)
Angina	2 (1.9)	10 (9.8)
Dislypidemia[b]	80 (75.5)	29 (40.8)
Glucose intolerance[c]	37 (34.9)	6 (5.9)

[a]Former smoker>1 year without smoking habitus.
[b]Total cholesterol>2.00 g/L and/or LDL>1.30 g/L and/or triglycerides>1.50 g/L.
[c]Fasting glucose>1.15 g/L; HbA_{1c}>6%.

The diagnosis of Arterial Hypertension (AH), according to European and JNC-VII guidelines,[44] was stated based on 24-hour ambulatory blood pressure monitoring (24-ABPM) results.

In studied group, baseline mean overall blood pressure (BP), mean systolic BP and mean diastolic BP were, respectively, 101.95 mmHg, 134.98 mmHg and 83.17 mmHg.

Glucose intolerance was defined according to American Diabetes Association criteria.[45]

Metabolic syndrome (MS) diagnosis was based on World Health Organization (WHO) clinical criteria.[46]

Antihypertensive medication were used by 53.3% (n=54) and 45.1% (n=32) patients and controls, respectively.

Antidiabetic medication were taken by 15.8% (n=16) of patients and by 7% (n=5) of controls.

Statins were taken by 37.6% (n=38) and 40.8% (n=29) of patients and controls, respectively.

Baseline Associations

In a univariate analysis, h-CRP levels at baseline correlated significantly with Apnoea/hypopnoea Index (AHI), desaturation index (DI) and with minimum oxygen saturation (Sat min 02) (table 5).

After adjustment for age, BMI, waist/hip, HDL cholesterol, glucose intolerance, AH and MS, no significant association remained between h-CRP and OSA severity indexes.

In a univariate analysis, IL-6 levels at baseline correlated significantly and negatively with Sat min 02 (table 5) but in a multivariate analysis, taking into account confounding factors found in this study for IL6 (waist/hip ratio), this relation turned to non significant.

We could not find any relation between baseline h-CRP and smoking habits, comorbidities like congestive heart failure (CHF), stroke, acute myocardial infarction (AMI), angina and sleepiness measured by Epworth scale.

We also could not see any relation between baseline IL-6 and age, BMI, cholesterol levels, smoking habits and comorbidities like glucose intolerance, MS, AH, AMI, stoke, CHF, angina and sleepiness measured by Epworth scale.

APAP effect on C-reactive protein and IL-6

Data is depicted in table 6.

We found no significant difference between h-CRP pre-treatment and in two moments post-treatment (9 days and 6 months) (*P*=.720

and *P*=.387, respectively) as also observed with IL-6 serum levels (*P*=.266, *P*=.238).

When we looked to h-CRP according to stablished categories related to cardiovascular (CV) risk (Fig. 1), we also could not see changes in those categories proportions when comparing moment pre-treatment with both two moments after treatment initiation (*P*=.623 and *P*=.872, respectively).

In patients under statins therapy the difference between h-CRP pre-treatment and 6 months after APAP was not significant (*P*=.872).

In non-sleepy patients the APAP effect on h-CRP and IL-6 was not different from that found in sleepy patients (*P*=.511 and *P*=.620, respectively).

Comparison of CRP at Baseline with Community Controls

h-CRP is significantly increased in patients when compared to controls (Fig. 2). According to h-CRP CV risk stratified categories, cases had significantly more patients at high risk of cardiovascular events than controls (Fig. 3).

After adjustment for BMI and AH, no significant association was found between risk of cardiovascular events and OSA patients (Table 8).

Discussion

The primary aim of our study was to assess the short and long term effect of APAP therapy on pro-inflammatory status in OSA patients.

Strong and consistent associations between levels of h-CRP and cardiovascular disease have been stablished in several studies across different population groups.[47] CRP is becoming an important biomarker for cardiovascular risk determination, even after adjustment for traditional risk factors typically used in cardiovascular risk-assessment programs.[22] The relationship between CRP and CV disease was further strengthened by the landmark finding that statins reduce plasma CRP and decrease the incidence of CV events.[48]

The baseline level of h-CRP in large-scale prospective studies[21] is an independent predictor marker for future CV events. Therefore, h-CRP level is both a risk factor for and an active pathogenic agent[49,50] in atherosclerosis.

Several studies[9] have shown a decrease in CRP levels with CPAP use in OSA patients, some[49] without a control group; but others[16,51,52] could not find a significant effect of long term CPAP on those levels. Neither ones nor the others have assessed statins use in the population analised.

Based on the available information relating to IL-6 in human diseases, serum IL-6 concentration seems to be a good indicator of activation of the inflammatory cascade and a predictor of subsequent organ dysfunction.[53]

Elevated concentrations of IL-6 predict total cardiovascular mortality over a 5-year follow-up, independently from traditional risk factors and stronger than, but additive to, that for CRP.[15]

Sleep apnoea has been associated with plasma IL-6[6,7] and h-CRP[10,11] elevations independently from obesity.

Contrary to previous literature, we found no correlation between the severity of OSA and the levels of IL-6 and h-CRP after multivariate analysis. However, differences in cytokine levels between moderate-severe OSA and mild OSA cannot be excluded, as the latter were not included in the present research. It can be speculated that beyond certain values of OSA severity, a linear correlation cannot be found,

Table 5
h-CRP (high sensitivity C- reactive protein) and IL-6 correlations at baseline

	h-CRP serum levels		IL-6 serum levels	
	r	*P*	r	*P*
Age	0.201	<0.001		
Body Mass Index	0.378	<0.001		
Waist/hip	0.339	<0.001	0.216	0.031
Glucose intolerance	0.346	<0.001		
Arterial hypertension	0.559	0.024		
Metabolic Syndrome	0.771	<0.001		
Apnoea/ Hypopnoea Index	0.237	0.027		
Dessaturation Index	0.315	0.004		
Sat min O_2	−0.234	0.032	−0.234	0.032
HDL cholesterol	−0.230	0.019		

HDL: high density lipoproteins.

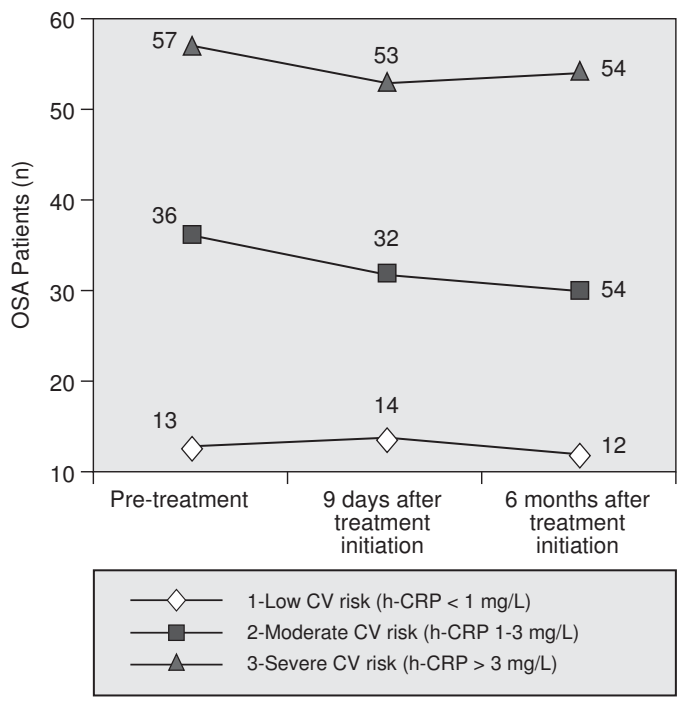

Figure 1. h-CRP distribution according to cardiovascular risk categories during study period in OSA patients.

Table 6
h-CRP and IL-6 mean serum levels before and after APAP therapy

	Pré-treatment	9 days after treatment initiation	p (Δ pré- 9 days)	6 months after treatment initiation	p (Δ 9days-6 months)
CRP (mg/dL)	0.52±0.53	0.63±0.92	0.720	0.54±0.92)	
IL-6 (pg/mL)	17.7±22.5	14.6±20.1	0.266	13.8±21.2	

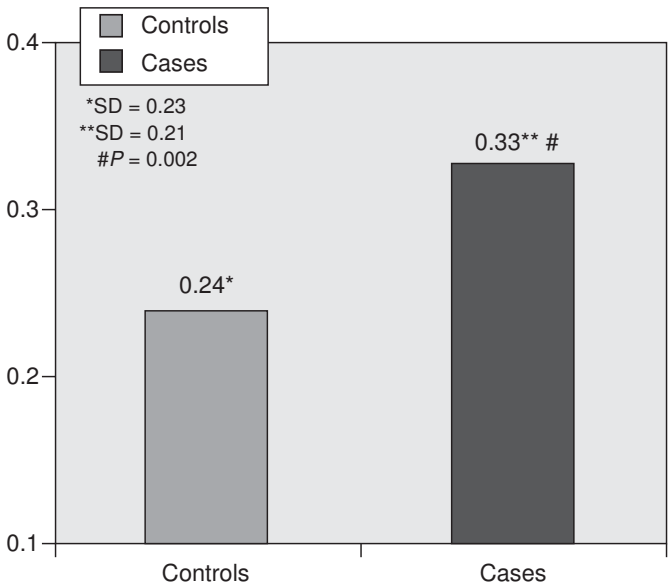

Figure 2. h-CRP serum levels (mg/dL) at baseline in cases and in controls.

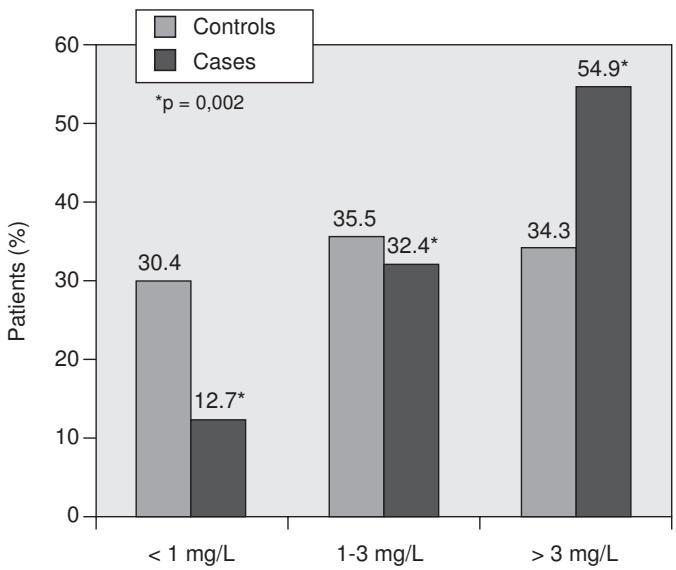

Figure 3. h-CRP distribution in CV risk categories among cases and controls.

Table 7
CV risk among OSA patients, according to h-CRP categories and compared with community controls

h-CRP	OR	Adjusted OR[a] (95% CI)
<1 mg/L	1	1[b]
1-3 mg/L	2.19 (0.98-4.87)	1.81 (0.78-4.23)
>3 mg/L	3.66 (1.64-8.18)	2.24 (0.94-5.30)

CI: confidence interval.
[a]OR adjusted for BMI and AH.
[b]Reference class.

suggesting that mechanisms others than hypoxia may be involved in increasing proinflammatory cytokines.

Also, different from other studies[10] relating h-CRP levels to OSA severity, our patients were older than those reported and since we found that h-CRP significantly correlates with age, we could speculate that older patients would have higher h-CRP, making the relation with OSA severity weaker.

We also could not observe relationship between sleepiness and IL-6 levels as others did.[6,54]

As far as we know there are only one study evaluating the APAP effect on h-CRP[39] and none on IL-6.

So, our study could add some evidence about APAP efficacy on reducing CV risk in OSA patients, as this therapy is a raising alternative approach to traditional CPAP able to improve symptoms[35] and patients compliance.[36]

In our study, short and long term APAP therapy was not able to decrease h-CRP and IL-6 serum levels. It is true that we cannot exclude that nighttime pressure variation in APAP is the reason why no decrease in h-CRP and IL-6 serum levels was observed but it is also true that many studies have not identified a decrease in h-CRP[51] and in IL-6[55] after CPAP use, especially when strong confounding factors as obesity were analysed.

The patients under statins did not show a different pattern of h-CRP response to APAP therapy than those not taking such a medication, differently from previous reports.[56,57]

As the studied population did not loose weight during the study period, we can speculate about being obesity the main predictor of h-CRP levels and IL-6 and not OSA as recent papers also sustained.[57]

On the other hand, the present study confirms that OSA is associated with elevated levels of h-CRP, a marker of inflammation and CV disease, as other studies could also demonstrate.[10] The heigtened h-CRP in these patients cannot be explained by other demographic or disease conditions since we have matched and adjusted cases and controls according to all those variables found to have a role in these relationship. The authors can also state, based on the results, that OSA patients have a two fold risk of being at moderate risk of CV events and more than a twofold risk of being at a severe risk of CV events when compared to controls.

Different from studies[10] relating h-CRP levels to OSA severity, our patients were older than those reported and since we found that h-CRP significantly correlates with age, we could speculate that older patients would have higher h-CRP, leading the relation with OSA severity weaker.

A possible limitation of our study is that it was not a randomized controlled trial. However, such a study is difficult to perform since it would be unethical to leave patients with confirmed OSA untreated.

Conclusions

In our study, OSA is associated with a low-grade inflammatory process; h-CRP serum levels are elevated in OSA patients when comparing to community controls, independently of age and BMI.

OSA patients have a significantly higher risk of cardiovascular events when compared to controls, according to h-CRP categories.

APAP therapy could not decrease both h-CRP and IL-6 after short and long-term treatment.

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Conflict of Interests

There are no financial or personal relationship with other people or organisation that could inappropriately influence this work.

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