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ORIGINAL ARTICLE

CRP evolution pattern in CPAP-treated obstructive sleep apnea patients. Does gender play a role?

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Abstract
Background—aim C-reactive protein (CRP) is directly implicated in atherogenesis and associated cardiovascular morbidity in patients with obstructive sleep apnea (OSA). Effective continuous positive airway pressure (CPAP) treatment has been shown to gradually decrease CRP levels and thus consequently improve disease-related cardiovascular morbidity. However, the influence of gender on the CRP evolution pattern has never been assessed before. The aim of our study was to investigate possible gender differences in CRP evolution in OSA patients 3 and 6 months after the start of effective CPAP treatment.
Methods The study population consisted of 436 patients (252 males/184 females) with newly diagnosed moderate to severe OSA and good CPAP compliance assessed by a thorough follow up. High-sensitivity C-reactive protein (hs-CRP) was assessed before CPAP initiation and at the third and sixth month of the follow-up period.
Results C-reactive protein values showed a statistically significant decrease at the third and sixth month of CPAP therapy [initial values 0.79±0.65 mg/dL versus 0.70±0.52 mg/dL ($p<0.05$) after 3 months and 0.30±0.33 mg/dL ($p<0.001$) after 6 months of CPAP therapy]. When patients were divided into males and females, the above evolution pattern was changed. At the third month time point, the CRP values showed a statistically significant decrease only in males (from 0.74±0.53 mg/dL to 0.61±0.5 mg/dL, $p<0.01$) while females showed only minimal and insignificant changes (from 0.87±0.79 mg/dL to 0.83±0.51 mg/dL, $p>0.05$). After 6 months' treatment, CRP decreased significantly in both genders (males from 0.74±0.53 mg/dL to 0.28±0.32 mg/dL, $p<0.001$ and females from 0.87±0.79 mg/dL to 0.34±0.36 mg/dL, $p<0.001$).
Conclusion Our results suggest a delay in the normalization of CRP levels in females despite effective CPAP treatment. A time period of at least 6 months appeared to be required in women in order to reduce CRP levels and consequent cardiovascular risk. In contrast, CPAP's protective role in males is achieved at an earlier time point. Gender-related hormonal and genetic factors may influence the above CRP evolution pattern.

Keywords C-reactive protein · Obstructive sleep apnea · CPAP · Gender

Charalampos Mermigkis and Izolde Bouloukaki made an equal contribution to this study.

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Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of complete or partial upper airway obstruction occurring during sleep [1]. These intermittent episodes disrupt normal ventilation and sleep architecture, initiating a range of pathophysiological mechanisms that may lead to cardiovascular disease. Indeed, OSA is an independent risk factor for a number of cardiovascular diseases, particularly systemic arterial hypertension [2, 3], coronary artery disease, congestive cardiac failure, and cerebrovascular events [4].

One important possible mechanism underlying cardiovascular disease in patients with OSA is systemic inflammation. In order to evaluate inflammation and predict the risk of vascular damage, several epidemiological studies have identified and measured circulating markers of inflammation, such as plasma cytokines, adhesion molecules, serum amyloid A, and C-reactive protein (CRP).

Of these markers, CRP has attracted special attention because assays to measure its levels are widely available in general hospitals and not only in specialized research laboratories [35]. C-reactive protein, an acute phase reactant secreted by the liver, is one of the most actively studied biomarkers of low-grade inflammation, and numerous studies have shown that higher CRP levels are associated with high mortality and morbidity due to cardiovascular disease in men and women [5–8]. It is worth noting that gender has been reported as a variable to consider in the analysis of CRP [9]. Several studies have also shown that women have higher CRP levels than men [10–12], probably because CRP levels increase to a greater degree with increasing adiposity in women than in men [10, 13].

In patients with OSA, the question as to whether or not CRP levels are elevated is still under debate, particularly because of the confounding impact of obesity and other cardiovascular diseases and medication on CRP levels. Some studies have demonstrated independent associations between CRP and OSA [14–21], whereas others do not show significant relationships after adjustment for relevant confounding variables [22–25]. Although continuous positive airway pressure (CPAP) is effective in the management of OSA, conflicting data also exist regarding the effects of CPAP on CRP levels. We and others have shown that effective CPAP treatment gradually decreases CRP levels and thus consequently improves disease-related cardiovascular morbidity [15, 26–29], while others found no significant change in CRP levels with CPAP therapy [22, 25, 30]. However, none of the abovementioned studies assessed the influence of gender on the CRP evolution pattern. Therefore, the aim of this study was to investigate possible gender differences in CRP evolution in patients with moderate to severe OSA, free of medical comorbitities, 3 and 6 months after the start of effective CPAP treatment.

Materials and methods

Patients

The study had a prospective design, including consecutive OSA patients recruited from three Greek sleep centers (the Sleep Disorders Units of the University Hospital of Heraklion, Crete; the General Army Hospital of Athens; and the Henry Dunant Hospital of Athens). Patients with a clinical suspicion of OSA were evaluated at the outpatient clinic of the participating sleep centers and scheduled for an overnight polysomnography (PSG). All subjects provided written informed consent, and ethical approval was provided by the participating Hospitals' Ethics Committees.

The patients had an interview and physical examination by a sleep specialist and completed the Epworth Sleepiness Scale (ESS). Exclusion criteria included comorbidities such as chronic obstructive pulmonary disease, diabetes mellitus, coronary artery disease, congestive heart failure, chronic renal failure, known dyslipidemia, smoking history, hypothyroidism, chronic or recent infectious or inflammatory disease, and use of anti-inflammatory or antibiotic drugs, or statins. None of the postmenopausal females included was on estrogen replacement therapy.

All included subjects underwent attended overnight PSG in order to identify possible underlying OSA. Patients with an apnea–hypopnea index (AHI) above 15 events per hour of sleep had a formal in-lab CPAP titration sleep study performed in accordance with the currently accepted guidelines [31]. Patients were thoroughly informed and trained by the sleep laboratory technicians in home CPAP use in order to achieve good compliance [32, 33]. The follow-up procedure included consecutive appointments (after 2 weeks and then monthly or whenever necessary in cases of CPAP-related problems) at the outpatient CPAP clinic. The use of CPAP was assessed by the CPAP card data at each appointment. Only patients who fulfilled the known CPAP good compliance criteria [32]—namely CPAP use more than 4 h per day and for more than 5 days per week—were finally included in the study protocol.

Polysomnography

Patients underwent a full diagnostic PSG study (Alice 5, Respironics), according to standard techniques, with monitoring of the electroencephalogram (EEG) using frontal, central, and occipital leads, electro-oculogram (EOG), electromyogram (EMG), flow (by oronasal thermistor and nasal air pressure transducer), thoracic and abdominal respiratory effort by uncalibrated impedance plethysmography belts, oximetry, and body position. Snoring was recorded by a microphone placed on the anterior neck. A

single modified type II EKG lead was used for cardiac monitoring.

Polysomnographic recordings were manually interpreted over 30-s periods, in accordance with the new AASM guidelines [34], and the scorer was blinded to the PSG findings of the first assessment. The determination of sleep stages and arousals was performed according to the AASM 2007 criteria and by using EEG montages including frontal, central, and occipital leads [34].

Blood collection and analysis

Venous blood was collected from all subjects for baseline hs-CRP measurements between 8:00 and 9:00 AM, following an overnight fast, shortly after the conclusion of the overnight sleep recordings (diagnostic of CPAP titration sleep study). At the third and sixth month of CPAP therapy, blood samples were drawn again for hs-CRP measurements in both groups. All venous samples were centrifuged and serum was separated into multiple aliquots and stored at −80° C until assay. CRP levels were measured by means of particle-enhanced immunonephelometry using BN Systems (Dade Behring Inc., Newark, USA). The lower CRP detection limit was 0.01 mg/dL.

Statistical analysis

Results are presented as means±SD. The Kolmogorov–Smirnov test was used to confirm normality. Differences between consecutive CRP values were assessed by a one-way analysis of variance (ANOVA) test with the Bonferroni correction. Demographic and polysomnographic data were compared between males and females using the unpaired *t* test (normally distributed data) or Mann–Whitney test (not normally distributed data). Statistical analysis was performed using SPSS 16 for Windows (Chicago, IL, USA). The significance criterion was defined at a p level <0.05

Results

We prospectively evaluated 740 patients (424 males/316 females) with suspected OSA who fulfilled the above-mentioned study inclusion criteria. All patients underwent attended overnight polysomnography in one of the participating sleep centers. Of the initial population, 160 were excluded as their apnea–hypopnea index (AHI) was either within normal limits or consistent with mild OSA (AHI <15/h sleep). All patients (n=580) with an AHI above 15 were started on CPAP after a formal CPAP titration sleep study and had an intensive follow-up at the CPAP clinic unit. No statistically significant differences were observed between males and females related to polysomnographic parameters of the CPAP titration study. C-reactive protein values were assessed at CPAP initiation and after 3 and 6 months of therapy (the last two measurements were performed only in the finally included patients). One hundred forty-four of the 580 initially included patients were excluded due to CPAP refusal or poor CPAP compliance, a change in body mass index (BMI) of >5% compared to baseline, or failure to keep the scheduled appointments at the CPAP clinic (flowchart in Fig. 1). Among the above excluded patients, the demographic and polysomnographic data were as follows: age (years)—39.4±12.1 vs. 47.8±12.9, p=0.002; BMI—29.4±3.8 vs. 30.9±7.3, p=0.20; and apnea–hypopnea index (AHI)—29.6±15.8 vs. 26.8±10.3, p=0.12 in males and females, respectively.

The baseline demographic and polysomnographic data of the 436 patients finally included are shown in Table 1.

Patients of both genders with moderate to severe OSA showed increased initial CRP values compared to subjects with no or mild OSA. No statistically significant differences were observed in initial CRP values between subjects with normal AHI and those with mild OSA, irrespective of gender (whole patient group—0.17±0.25 mg/dL vs. 0.19±0.35 mg/dL, p=0.39; males—0.14±0.22 mg/dL vs. 0.17±0.26 mg/dL, p=0.21; females—0.20±0.27 mg/dL vs. 0.25±0.32 mg/dL, p=0.29). When absolute CRP values were compared, females with moderate to severe OSA had higher values compared to males, although the differences were not statistically significant. A possible reason might be related to the higher BMI of the females compared to males (Table 1).

Initiation of CPAP therapy showed a difference in the evolution of CRP values between the two genders. Males showed a significant decrease after 3 months of therapy, whereas at the same time point CRP remained unchanged in females, despite the carefully observed good CPAP compliance (initial and 3-month CRP values 0.74±0.53 mg/dL vs. 0.61±0.5 mg/dL, p<0.01 in males and 0.87±0.79 mg/dL vs. 0.83±0.51 mg/dL, p>0.05 in females, respectively). A different profile was seen at the 6-month time point of CPAP therapy, where a marked decline in CRP was seen in both genders (initial and 6-month CRP values 0.74±0.53 mg/dL vs. 0.28±0.32 mg/dL, p<0.001 in males and 0.87±0.79 mg/dL vs. 0.34±0.36 mg/dL, p<0.001 in females, respectively). The data are summarized in Figs. 2 and 3.

Discussion

This is the first study to report gender-related differences in the CRP evolution pattern in OSA patients who are under CPAP treatment. Three months of effective CPAP therapy based on currently accepted “good CPAP compliance”

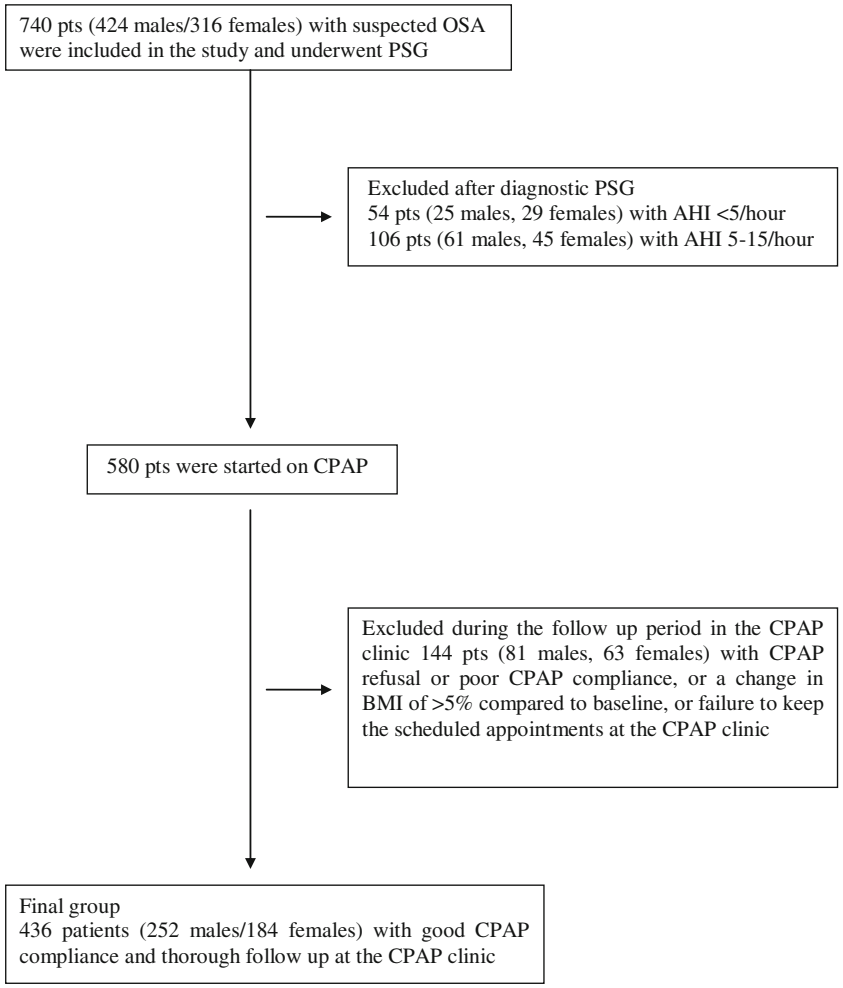

Fig. 1 Flowchart showing the patient selection process

criteria is not adequate to normalize hs-CRP values and consequent cardiovascular risk in females, in contrast to males with OSA of similar severity.

C-reactive protein is a well-recognized factor of systemic inflammation seen in OSA [14, 16, 20, 23]. Previous studies have shown that obesity as well as OSA severity assessed by a variety of polysomnographic parameters such as the AHI, desaturation, and/or arousal indices are the main factors that influence CRP values in these patients. Current evidence suggests that hs-CRP is the most appropriate inflammatory marker in daily clinical and public health practice for reasons related to accuracy,

Table 1 Demographic–polysomnographic data and initial C-reactive protein values of the patients included in the study

	Total patients (n=436)	Males (n=252)	Females (n=184)	p value (males vs. females)
Age (years)	53.2±11.7	50.9±12.2	56.3±10.3	<0.0001
BMI (kg/m^2)	35.2±7.3	33.7±6.5	37.4±7.4	<0.0001
N/C (cm)	42.1±3.9	43.8±3.6	39.9±3.3	<0.0001
ESS score	16.7±4.9	17.2±4.7	13.1±4.3	<0.0001
AHI (events/h)	44.5±23.1	45.6±22.5	42.9±23.8	0.11
Arousal index (arousals/h)	37.9±14.6	39.7±15.7	35.4±14.1	0.003
Oxygen desaturation index	40.8±22.6	41.8±21.9	38.8±23.7	0.10
Lowest SaO_2 (%)	75.1±9.6	75.5±9.4	76.9±9.9	0.11
Mean SaO_2 (%)	87.8±5	87.4±5.1	88.3±4.8	0.09
CRP (mg/dL)	0.79±0.65	0.74±0.53	0.87±0.79	0.53

AHI apnea/hypopnea index, *BMI* body mass index, *N/C* neck circumference, *ESS* Epworth Sleepiness Scale, *SaO_2* oxygen saturation

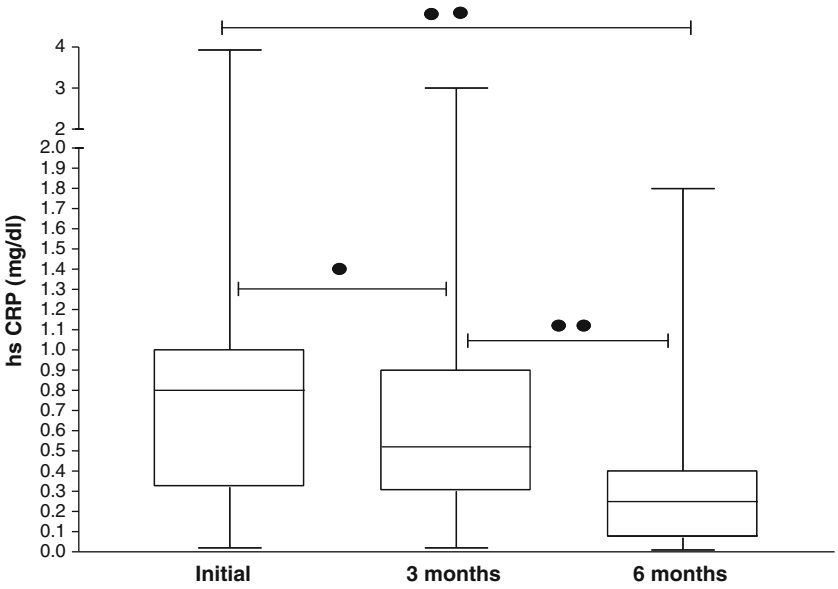

Fig. 2 Hs-CRP evolution in males. *Box plot* showing CRP values before, 3 months, and 6 months after CPAP therapy. *Bottom and top of the box* are 25th and 75th percentiles, and the *error bars outside the box* represent maximum and minimum values, respectively. *Black circle*: $p<0.01$, *double black circles*: $p<0.001$

availability, and standardization [35]. The association of hs-CRP with vascular events provides a strong argument for screening in the primary prevention population [36, 37]. Women generally have higher CRP levels than men, but the mechanisms behind this observation are unknown [10–12, 38].

A decline in hs-CRP after initiation of CPAP therapy has been reported previously, and CPAP compliance was recognized as a crucial factor in CRP evolution and associated cardiovascular risk [15, 26–29]. On the other hand, there are no studies related to possible gender influences on the profile of CRP evolution during OSA treatment with CPAP. Our study shows a markedly different profile between males and females with OSA of the same severity. C-reactive protein values in females remained virtually unchanged during the first 3 months, despite successful CPAP treatment, whereas males showed a significant decrease in CRP over the same period. At the 6-month time point, a significant decrease was seen in all patients who continued CPAP, with CRP values approaching those of subjects without OSA.

The main question that arises is related to the reason for the delay in CRP decrease after CPAP initiation in females compared to males with no differences in OSA severity. Despite the clinical improvement and the good CPAP compliance, the elevated CRP values during the first

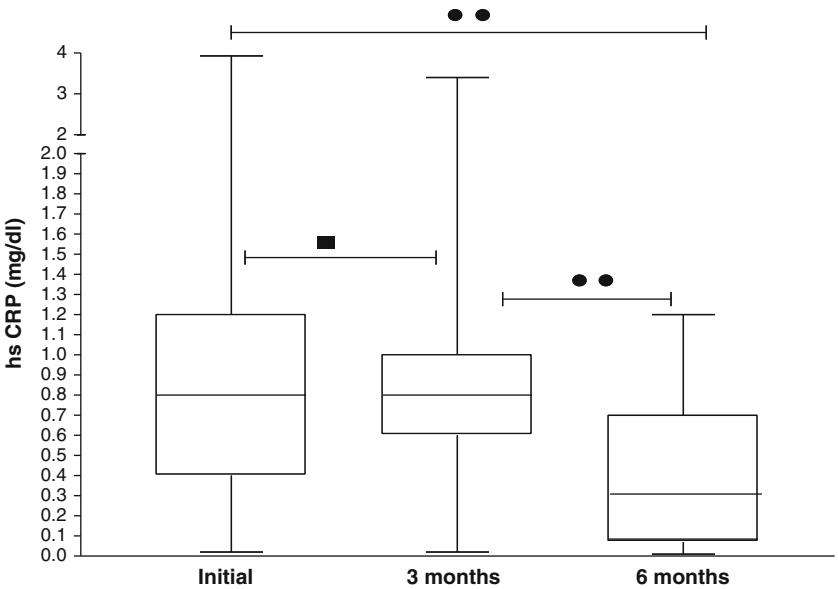

Fig. 3 Hs-CRP evolution in females. *Box plot* showing CRP values before, 3 months, and 6 months after CPAP therapy. *Bottom and top of the box* are 25th and 75th percentiles, and the *error bars outside the box* represent maximum and minimum values, respectively. *Black square*: $p>0.05$ (non-significant), *double black circles*: $p<0.001$

3 months of CPAP showed a residual inflammatory process in females and diminished protection against the known deleterious cardiovascular complications of OSA. This female profile might be the result of gender-related hormonal factors that delay the normalization of CRP. An obvious question is whether the generally accepted good compliance rules of more than 4 h per day and more than five nights per week [32, 33] may not be appropriate for females with moderate to severe OSA, at least during the first months of CPAP therapy. Sleep center physicians should probably make a more intense effort in order to access an increase in CPAP use in females with moderate to severe OSA above the generally accepted rules of "good" compliance.

Obstructive sleep apnea may be poorly and belatedly recognized in women due to differences in their clinical profile and the well-known lower incidence of the syndrome in the pre-menopausal period [39, 40]. The mean age of females included in our study was greater compared to males, and this might be related to the abovementioned factors. Disease severity based on the AHI or nocturnal oxygenation parameters was without significant differences between males and females, but the underlying inflammatory process in females might be more intense than in males and its resolution could thus require a longer period of effective CPAP therapy.

C-reactive protein is only one factor related to the underlying deleterious inflammatory process in OSA. However, daily clinical practice needs simple, standardized, and cost-effective methods for patient follow-up, and hs-CRP offers these characteristics. In the current existing clinical guidelines [35], CRP was included as a part of a global risk-prediction strategy, which suggested that levels of hs-CRP of <0.1, 0.1 to <0.3, and ≥0.3 mg/dL be used to represent low, moderate, and high vascular risk. In this way, CRP might be useful together with all other parameters (clinical course, data from the CPAP device, etc.) that are used in CPAP clinics during the follow-up of patients with OSA. This might be of additional importance in females based on our data showing a refractory inflammatory process during the initial 3 months of CPAP use.

In conclusion, this is the first study to evaluate gender differences in the CRP evolution pattern in patients with OSA who are under CPAP therapy. Females show a delay in the normalization of CRP compared to males, which indicates a refractory inflammatory process despite effective CPAP therapy. It is well known that OSA has a different profile in females as regards clinical presentation and diagnostic procedure. Our data offer new insight into the generally accepted therapeutic approach with CPAP. Further studies are necessary to recognize "how much CPAP" is necessary in females with OSA in order to reduce inflammation and consequent disease-related cardiovascular risk.

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