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Original article

Obesity, and not obstructive sleep apnea, is responsible for increased serum hs-CRP levels in patients with sleep-disordered breathing in Delhi

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Abstract

Objective: The present study was conducted to evaluate serum levels of high-sensitivity C-reactive protein (hs-CRP) in newly diagnosed patients with obstructive sleep apnea (OSA).
Subjects and methods: Between April 2005 and March 2006, a total of 231 consecutive adult habitual snorers underwent polysomnography (PSG) in the sleep laboratory. Ninety-seven subjects were found suitable for hs-CRP measurement after application of the following exclusion criteria: patients with diabetes mellitus, hypertension, coronary artery disease, acromegaly, hypothyroidism, chronic renal failure, congestive cardiac failure, or smoking history, patients who were pregnant, on steroid treatment, on hormone replacement therapy, or with chronic use of drugs such as non-steroidal anti-inflammatory drugs, oral anticoagulants and lipid-lowering drugs and patients having undergone upper airway surgery. Patients were classified as apneic [apnea–hypopnea index (AHI) > 5], obese non-apneic [body mass index (BMI) > 25, AHI < 5] and non-obese non-apneic (BMI < 25, AHI < 5). C-reactive protein levels were measured in stored sera by high-sensitivity enzyme immunoassay (Biocheck, Inc. Foster City, CA, USA). After checking normality with the Kolmogorov–Smirnov test and using a square-root transformation, Pearson's and partial correlation coefficients were calculated for identified risk factors and confounders. A multiple linear regression model was used to identify variables that were independently associated with hs-CRP.
Results: The mean serum levels of hs-CRP were found to be 0.25 ± 0.23, 0.58 ± 0.55, and 0.51 ± 0.37 mg/dl in non-obese non-apneics ($n = 23$), obese non-apneics ($n = 45$) and apneics (obese and non-obese, $n = 29$), respectively. Pearson's correlation coefficient of hs-CRP with BMI was found to be 0.25 ($p = 0.01$), and with AHI 0.16 ($p = 0.12$). Partial correlation analysis showed that hs-CRP levels correlated significantly with BMI after adjustment for AHI and age ($r = 0.22$, $p = 0.03$), while correlation with disease severity as assessed by AHI after adjustment for BMI and age was not significant ($r = 0.10$, $p = 0.33$). After stepwise multiple linear regression, only BMI was found to be significantly associated with serum hs-CRP levels ($\beta = 0.02$, $p = 0.01$).
Conclusions: In this first comprehensive cross-sectional study on Indian subjects, we found that obesity, and not obstructive sleep apnea, is associated with elevated serum levels of hs-CRP. No independent correlation was found between severity of OSA and hs-CRP in the present study.
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Keywords: Obstructive sleep apnea; Polysomnography; High-sensitivity C-reactive protein; hs-CRP; Obesity

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1. Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive episodes of partial or complete obstruction of the upper airway during sleep, with consequent sleep fragmentation and decreased oxygen saturation. A potential mechanistic link between OSA and atherogenesis is related to recurrent episodes of repetitive surges of sympathetic activity, blood pressure, and oxidative stress produced during these episodes [1]. Recent findings have indicated that OSA is associated with multiple causal factors of endothelial damage and atherosclerosis [2]. It has been suggested that OSA-related hypoxia and systemic inflammation might be associated with the progression of atherosclerosis and thus might increase the risk for cardiovascular and cerebrovascular morbidity in patients with OSA [3–5].

Though OSA was long believed to be a disease of the affluent nations, its occurrence is being increasingly recognized in the developing world. In the only community-based study from the region, the prevalence of OSA and obstructive sleep apnea syndrome (OSAS) has been reported as 13.74% and 3.57%, respectively, in an urban Indian population [6].

Several studies have suggested that increased serum levels of C-reactive protein (CRP), interleukin (IL)-6, and tumor necrosis factor (TNF)-α are important risk factors for atherosclerosis, stroke, and cardiovascular diseases [7–9]. Recent studies have demonstrated elevated serum levels of CRP, IL-6, and TNF-α in OSA [10,11]. Moreover, it has been suggested that increased levels of circulating soluble adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), chemokines, such as monocyte chemoattractant protein-1 (MCP-1), and vascular endothelial growth factor in OSA might accelerate the progression of atherosclerosis [12–14].

C-reactive protein (CRP), a member of the pentraxin family of proteins is an important marker of endothelial dysfunction in the pathogenesis of coronary artery disease [15–18]. It is produced predominantly by the liver under the control of IL-6. However, IL-1 and TNF-α also contribute to its hepatic synthesis and secretion. Recent studies suggest that CRP is also produced in atherosclerotic lesions, kidney, neurons, alveolar macrophages, and adipose tissue [19–23]. It is transported freely in plasma and activates complement and binds to Fc receptors, which may facilitate the uptake and clearance of apoptotic and necrotic cells during the acute phase response [19–21,24–26]. It has a half-life of approximately 19 h. CRP is a prototype inflammatory marker, which may play a direct role in atherogenesis and thrombus formation. In addition to OSA, several other conditions that are associated with increased levels of CRP include chronic inflammation, obesity, metabolic syndrome, type 2 diabetes mellitus, and hypertension. Conflicting reports of serum CRP levels have been published in OSA [10–18,21,22]. The present study compares the serum levels of hs-CRP in apneic and non-apneic subjects.

2. Methods

This study was conducted between April 2005 and March 2006 in the Department of Medicine at the All India Institute of Medical Sciences Hospital, New Delhi, India. The Ethics Committee of the hospital approved the study. Subjects who, during sleep studies at the sleep laboratory, were found to have OSA were included in the study. In addition, non-apneic subjects were recruited from an ongoing community-based prevalence study. Written informed consent was obtained from all participants. A modified version of Wisconsin Sleep Cohort Questionnaire (*courtesy: Young T, USA*) [27] that included questions about demographics, sleep symptoms, medical history, and medications, was completed for all subjects recruited. A flow diagram of the study subjects is presented in Fig. 1.

Subjects who had known diabetes mellitus, hypertension, coronary artery disease, acromegaly, hypothyroidism, chronic renal failure, or congestive cardiac failure, who were pregnant, on steroid treatment, on hormone replacement therapy, or with chronic use of drugs such as non-steroidal anti-inflammatory drugs, oral anticoagulants and lipid-lowering drugs, who had undergone upper airway surgery, or who had a history of smoking and alcohol consumption were excluded from the study.

A limited physical examination was performed in which height, weight, body mass index (BMI), neck circumference, waist and hip girth, waist–hip ratio, and blood pressure were measured [23,28,29]. Body composition was measured by Tanita body composition analyzer (model TBF-300; TANITA France, Neuilly-sur-Seine, France). Subjects were considered hypertensive if they were currently receiving antihypertensive medication or if they had a blood pressure greater than 140/90 mmHg, measured as a mean of two readings taken with the subject seated in a quiet room, satisfying the Joint National Committee (JNC 7) criteria for hypertension [30]. The disappearance of Korotkoff's sounds was used as a criterion for the measurement of diastolic measurement. Subjects were classified as obese when BMI was $\geqslant 25\ kg/m^2$, as defined by the World Health Organization for the Southeast Asia region [31]. The entire group was analyzed for hs-CRP and demographic parameters, and the association with OSA was studied.

2.1. Polysomnography (PSG)

PSG studies, conducted in the sleep laboratory (Alice 3 system; Healthdyne), consisted of continuous polygraphic recording from surface leads for electroenceph-

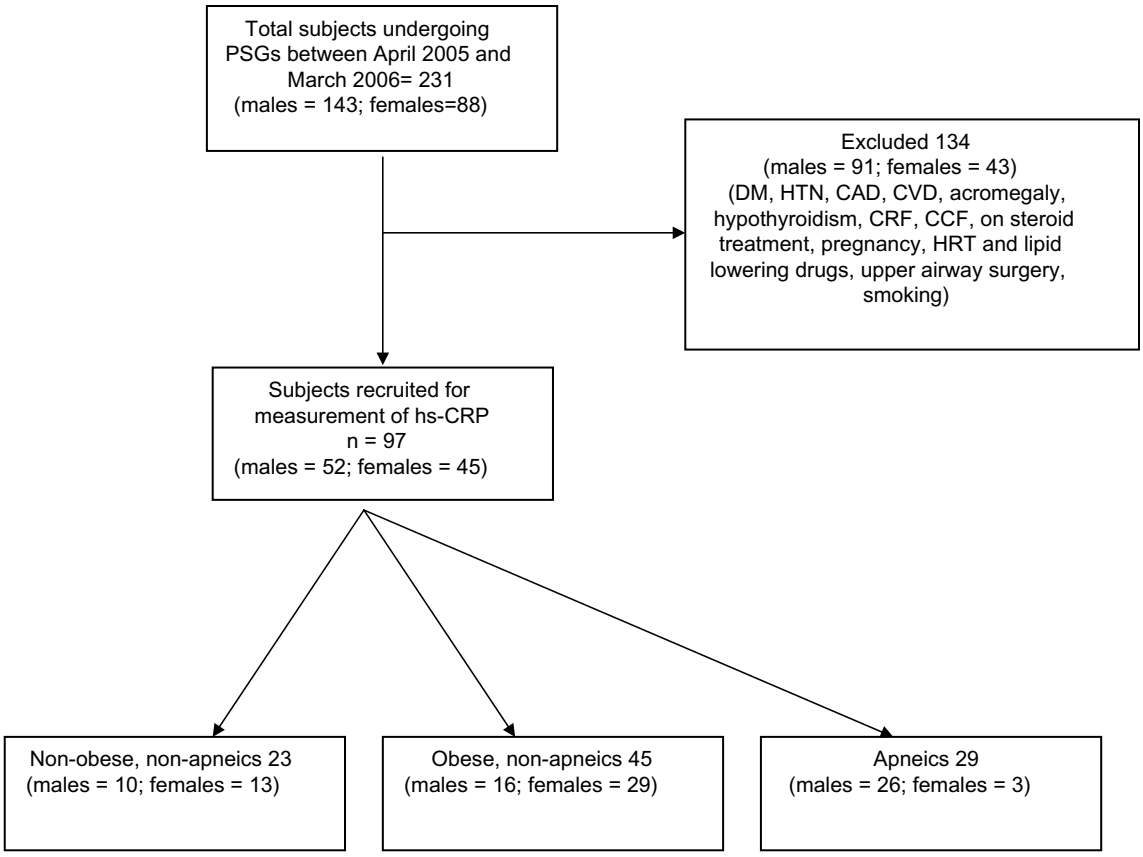

Fig. 1. Flow diagram of the study. *Abbreviations:* PSG, polysomnography; DM, diabetes mellitus, HTN, hypertension; CAD, coronary artery disease; CVD, cardiovascular disease; CRF, chronic renal failure; CCF, congestive cardiac failure; HRT, hormone replacement therapy; hs-CRP, high-sensitivity C-reactive protein.

alogram (EEG), electro-oculography (EOG), electromyography (EMG), electrocardiogram (ECG), thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory efforts, pulse oximetry for oxyhemoglobin level, and tracheal microphone for snoring and sensors for leg and sleep position [28]. PSG records and sleep data were scored according to standard criteria [32]. Apnea was defined as complete cessation of airflow lasting 10 s or more; hypopnea was defined as either a >50% reduction in airflow for 10 s or more or less than 50% but discernible reduction in airflow accompanied either by a decrease in oxyhemoglobin saturation of >3% or an arousal. The apnea–hypopnea index (AHI) was calculated and the subjects were labeled OSA (apneic) if they had AHI > 5. Arousals were identified according to established criteria [33]. Excessive daytime sleepiness (EDS) was assessed based upon the subject's response to eight questions regarding probability of dozing off in specific situations. Using a four-point scale, the Epworth sleepiness scale (ESS) score was calculated [34]. A score >10 was considered suggestive of EDS. OSAS was defined as presence of EDS with an AHI > 5. The subjects were grouped as non-obese non-apneic (AHI < 5 and BMI < 25), obese non-apneic (AHI < 5 and BMI > 25) and apneic (AHI > 5).

2.2. hs C-reactive protein (hs-CRP)

Venous blood was collected between 6:30 and 7:00 am after overnight PSG, and the serum was isolated within the next hour. After separation, the serum was stored at −80 °C until analysis. Serum C-reactive protein was measured by high-sensitivity enzyme immunoassay [Biocheck, Inc. Foster City, CA, USA; coefficients of variation: inter-assay < 10.8, intra-assay < 9.3; (as provided by the manufacturer)] for the quantitative determination.

2.3. Statistical analysis

Data were collected on a pre-designed proforma and were analyzed with SPSS 11.5 statistical software (SPSS, Inc. Chicago, USA). Quantitative variables were expressed as the means ± standard deviation (SD) after checking normality with the Kolmogorov–Smirnov test. The hs-CRP levels were positively skewed and a square-root transformation was used. Pearson's and partial

correlation coefficients between hs-CRP levels and BMI and AHI were obtained. Serum levels of hs-CRP were used as the dependent variable and age, total cholesterol, triglyceride, HDL cholesterol, BMI, and AHI as the independent variables in a multiple linear regression analysis model to identify variables that were independently associated with hs-CRP. A value of $p < 0.05$ was considered statistically significant.

3. Results

A total of 231 subjects underwent PSG in the sleep lab during the study period. After applying strict exclusion criteria, 97 subjects were considered suitable for hs-CRP measurement. The comparative profile of the subjects is provided in Table 1.

The mean serum levels of hs-CRP were found to be 0.25 ± 0.23, 0.58 ± 0.55, and 0.51 ± 0.37 mg/dl in non-obese non-apneics ($n = 23$), obese non-apneics ($n = 45$), and apneics ($n = 29$), respectively. Sleep study parameters of the various study groups are shown in Table 2.

The Pearson's correlation coefficient of hs-CRP with BMI was found to be 0.25 ($p = 0.01$), and with AHI 0.16 ($p = 0.12$). Coefficients of correlation between various parameters are provided in Table 3. Partial correlation analysis showed that hs-CRP levels correlated significantly with BMI after adjustment for AHI and age ($r = 0.22$, $p = 0.03$), while correlation with disease severity as assessed by AHI after adjustment for BMI and age was not significant ($r = 0.10$, $p = 0.33$). The association between hs-CRP and AHI is shown in Fig. 2 and that between hs-CRP and BMI is shown in Fig. 3. On subgroup analysis, we found that there was a significant correlation between BMI and hs-CRP in females after adjustment for AHI and age ($r = 0.40$, $p < 0.01$), but no correlation was observed between AHI and hs-CRP after adjustment for BMI and age ($r = 0.03$, $p = 0.83$). Among males, no significant correlation was seen either with AHI ($r = 0.21$, $p = 0.14$) or BMI ($r = 0.01$, $p = 0.96$).

After stepwise multiple linear regression, only BMI was found to be significantly associated with serum hs-CRP levels ($\beta = 0.02$, $p = 0.01$).

4. Discussion

Since the initial report of raised levels of CRP in OSA appeared in the literature [35], the role of obesity as a confounder in the association between OSA and surrogate markers of inflammation such as CRP, TNF-α, and IL-6 among others has generated a considerable debate [22,35–40]. It would be desirable to compare a cohort of obese apneics with non-obese apneics after careful exclusion of potential confounders to arrive at the actual answer. However, in clinical practice, apneic individuals

Table 1
Baseline characteristics of the study groups ($n = 97$)

Variables	Non-obese non-apneics ($n = 23$)	Obese non-apneics ($n = 45$)	Apneics[d] ($n = 29$)	p value
Age (years)	40.52 ± 9.57	41.2 ± 9.24	45.28 ± 8.59	0.11
Males (%)	10 (43.48%)	16 (36.56%)	26 (89.66%)	<0.001[a,b]
BMI (kg/m^2)	21.56 ± 2.49	29.38 ± 3.34	29.17 ± 4.02	<0.001[b,c]
Free fat mass (kg)	41.37 ± 7.94	44.54 ± 10.14	53.08 ± 9.03	<0.001[a,b]
Total body water (kg)	30.3 ± 5.78	32.62 ± 7.43	39.43 ± 6.50	<0.001[a,b]
TSFT (mm)	16.52 ± 7.35	22.49 ± 7.97	18.21 ± 6.02	0.003[a]
BSFT (mm)	9.00 ± 3.67	14.80 ± 5.83	13.38 ± 5.45	<0.001[a,b]
SSFT (mm)	20.96 ± 5.49	27.00 ± 6.94	24.07 ± 5.57	0.001[c]
SIFT (mm)	25.43 ± 8.47	30.51 ± 6.88	27.79 ± 5.91	0.02[c]
Neck circumference (cm)	33.22 ± 4.88	35.04 ± 4.61	39.62 ± 3.79	<0.001[a,b]
Waist–hip ratio	0.93 ± 0.09	0.97 ± 0.07	1.01 ± 0.06	<0.001[b,c]
Systolic blood pressure (mmHg)	122.17 ± 7.13	125.47 ± 8.23	124.14 ± 6.19	0.23
Diastolic blood pressure (mmHg)	79.52 ± 6.85	81.11 ± 5.09	81.93 ± 2.53	0.22
Epworth sleepiness scale	3.57 ± 3.42	3.89 ± 3.05	13.55 ± 6.31	<0.001[a,b]
AHI (events/h)	0.23 ± 0.84	0.71 ± 1.45	48.64 ± 26.02	<0.001[b,c]
Triglyceride (mg/dl)	145.19 ± 53.80	137.85 ± 53.81	150.96 ± 111.72	0.78
Total cholesterol (mg/dl)	175.24 ± 30.93	183.78 ± 45.17	184.12 ± 39.09	0.69
HDL cholesterol (mg/dl)	46.48 ± 11.22	44.63 ± 8.63	37.63 ± 4.73	0.001[a,b]
Fasting blood sugar (mg/dl)	94.22 ± 14.57	95.67 ± 9.82	89.66 ± 9.08	0.07
hs-CRP (mg/dl)	0.25 ± 0.23	0.58 ± 0.55	0.51 ± 0.37	0.02[c]

Data are expressed as means ± SD or No. (%), unless otherwise indicated.
Abbreviations: BMI, body mass index; AHI, apnea–hypoapnea index; hs-CRP, high sensitivity C-reactive protein; TSFT, triceps skin fold thickness; BSFT, biceps skin fold thickness, SSFT, subscapular skin fold thickness; SIFT, subiliac fold thickness; HDL, high density lipoprotein.
[a] $p < 0.05$ between apneics and obese non-apneics.
[b] $p < 0.05$ between apneics and non-obese non-apneics.
[c] $p < 0.05$ between obese and non-obese non-apneics.
[d] Three subjects were non-obese apneics (BMI < 25, AHI > 5).

Table 2
Comparison of polysomnography parameters between three groups ($n = 97$)

Parameters	Non-obese non-apneics ($n = 23$)	Obese non-apneics ($n = 45$)	Apneics ($n = 29$)	p value
Baseline SaO_2 (%)	96.3 ± 1.99	96.38 ± 1.95	94.69 ± 2.32	<0.01[a,b]
Minimum SaO_2 (%)	91.75 ± 2.17	89.92 ± 2.46	66.48 ± 16.24	<0.001[a,b]
$SaO_2 < 90\%$ (%)TST	0.40 ± 1.26	0.95 ± 1.50	23.59 ± 22.25	<0.001[a,b]
Arousal index/h	5.92 ± 6.02	4.79 ± 5.87	16.07 ± 9.72	<0.01[a,b]
Total sleep time (min)	343.22 ± 75.11	352.04 ± 71.64	383.90 ± 77.23	0.10

*Values are given as the means ± SD, unless otherwise indicated.
Abbreviations: SaO_2, arterial oxygen saturation; TST, total sleep time.
[a] $p < 0.05$ between OSA and obese non-apneics.
[b] $p < 0.05$ between OSA and non-obese non-apneics.

who are not overweight are encountered infrequently, and it may take many years to construct a sizable cohort of such patients. Working in the constraints of clinical practice, for a precise estimation of the actual role of obesity in the raised levels of markers of inflammation found in subjects with OSA, a sample devoid of known confounders is essential. However, most contemporary studies have failed to completely exclude confounding factors while addressing the issue [22,35,36,40–42].

Table 3
Pearson's and partial correlation of hs-CRP with various variables

Variables	Pearson's correlation (p value)	Partial correlation[a] (p value)
Age (years)	0.06 (0.56)	–
BMI (kg/m^2)	0.25 (0.01)[b]	0.22 (0.03)[b]
AHI (events/h)	0.16 (0.12)	0.10 (0.33)
Min SaO_2 (%)	−0.08 (0.47)	–
$SaO_2 < 90\%$ (%) TST	−0.003 (0.98)	–

Abbreviations: BMI, body mass index; AHI, apnea–hypoapnea index; hs-CRP, high-sensitivity C-reactive protein; SaO_2, arterial oxygen saturation; TST, total sleep time.
[a] Adjusted for Age and AHI for correlation between hs-CRP and BMI; adjusted for Age and BMI for correlation between hs-CRP and AHI.
[b] Significant.

The current cross-sectional study assessed the association of serum hs-CRP with OSA in Indian subjects for the first time, with strict elimination of all known confounding factors (e.g., hypertension, diabetes, established coronary artery disease, cerebrovascular disease, smoking, and trauma). We found a significant correlation of hs-CRP with BMI after adjusting for age and AHI. In females with increased BMI, hs-CRP was found to be significantly increased ($r = 0.40$, $p < 0.01$) in concordance with the previous reports of a progressive rise of CRP levels with BMI in healthy females [43]. The current study assumes importance in view of the fact that an alarming rise in the prevalence of obesity has been closely followed by the recognition of OSA on the Indian subcontinent [6]. According to World Health Organization statistics, 25.4% of urban Indian men and 35.8% of women are obese [44]. Besides a scarcity of data, it has been postulated that coronary artery disease and lipid abnormalities behave differently in the Indian population in comparison to our Western counterparts [45]. Several authors have reported findings similar to our results [22,40].

In a large cross-sectional case-control design, Guilleminault et al. studied the hypothesis that if OSAS patients with normal weight have an abnormal CRP

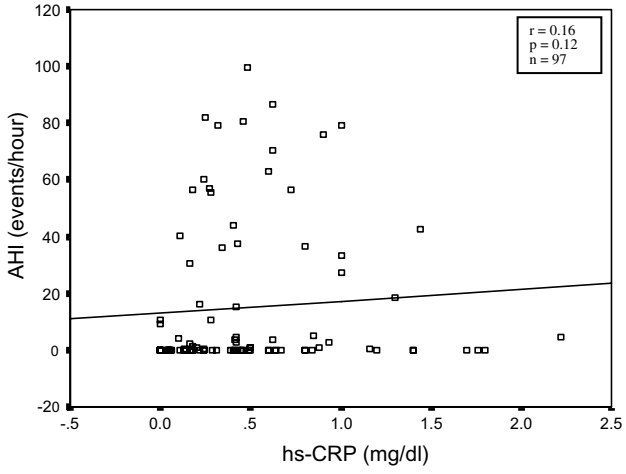

Fig. 2. Correlation between AHI (events/h) and hsCRP (mg/dl).

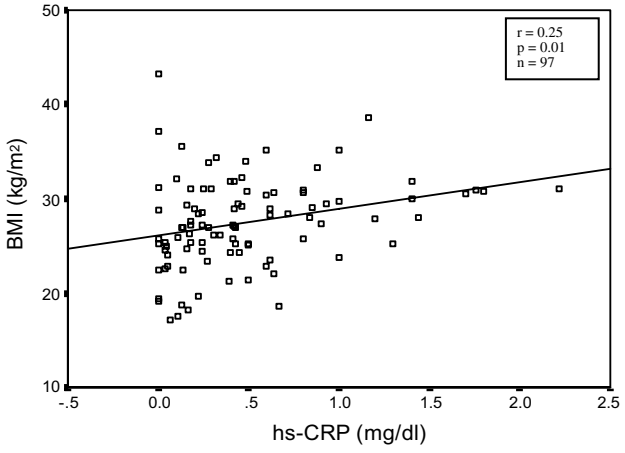

Fig. 3. Correlation between BMI (kg/m^2) and hsCRP (mg/dl).

then the rise in CRP may not be due to obesity [22]. They successively monitored 239 participants and observed that CRP levels remained normal in most patients, except in a small minority. After a regression analysis, with CRP as the dependent variable regressed on BMI, age, sex, respiratory disturbance index (RDI), and lowest SaO_2, the authors reported that CRP levels correlated only with BMI, suggesting the confounding role of obesity [22].

Saletu et al. studied the association between common carotid atherosclerosis detected by ultrasonography and serum surrogate markers and the polysomnographically measured severity of OSA in 147 subjects [40]. The authors found significant differences in levels of hs-CRP between the control group and the severe OSA group (AHI > 30), but after correction for confounders (BMI, age, systolic blood pressure, and HbA_{1c}) these differences were no longer significant. Interestingly, in their study, more subjects in the OSA group were on antihypertensive, oral hypoglycemic, and lipid-lowering agents than the non-OSA group. After regression analysis, only BMI was found to correlate with serum hs-CRP levels.

However, several reports are at variance with the confounding role of obesity and have indicated a significant correlation of OSA with raised serum levels of CRP, independent of obesity [35,36,41]. Shamsuzzaman et al. first reported a correlation between plasma levels of CRP and OSA, after studying 22 patients with severe OSA and comparing them with 20 control subjects matched for age and BMI [35]. Interestingly, in their study, the controls were younger, thinner, had a lower frequency and amount of alcohol consumption and cigarette smoking, and had a lower mean blood pressure, heart rate, lipid levels at baseline, although these differences were individually insignificant. A proportion of subjects with OSA and controls had smoking history. Ideally, smokers should have been excluded, as smoking is known to be associated with elevated CRP levels. Additionally, their study does not provide any information about blood sugar levels.

Kokturk et al. studied serum CRP levels in 173 obese male subjects in a case-control design, in three groups: those with OSAS and cardiovascular disease (CVD, hypertension, and ischemic heart disease) compared with those without OSAS or CVD, respectively [41]. They concluded that serum CRP levels correlated positively with OSAS. However, they did not take into consideration the details of the previous medications taken by the subjects, which could have affected the levels of CRP. Can et al. studied dyslipidemia along with levels of CRP in the serum in 62 male patients in a case-control study [36]. They revealed significant differences in the levels of CRP and homocysteine between the two groups. Several methodological concerns need to be addressed with regard to their study design, including the absence of detailed information about comorbid illnesses, medication use, and gender of the control group.

Zouaoui et al. studied clinical characteristics in 49 patients with sleep apnea and reported correlation between AHI and CRP ($r = 0.43$). They suggested that AHI was an independent risk factor for cardiovascular risk [42]. The authors reported that they were working in a real-life situation in a general hospital, and hence a number of patients did not accept the study, or were not included because they did not understand the study. This could have created a strong selection bias. Moreover, their study design does not provide any insight into non-apneic individuals included in their study. It is noteworthy that in their study BMI was not found to correlate with levels of CRP, an observation not reflected in other contemporary studies.

In a previous study, while studying the association of metabolic abnormalities with OSA, obesity was found to be the major determinant of metabolic abnormalities [37]. In the current study, our results indicate that obesity plays a strong confounding role in the association between hs-CRP and OSA. One possible explanation for the conflicting results is that the magnitude of inflammatory response to OSA observed in some patients may be indicative of particular subgroups at increased risk for development of long-term cardiovascular complications. Besides, it has been suggested that not only the severity but the duration of the disease could also influence the elevation of hs-CRP [42].

Our study reiterates the assertion that obesity is a confounding factor in most reports of association between hs-CRP and OSA. Future research should carefully assess the role of obesity in OSA before labeling hs-CRP as an independent marker of OSA, in rigorously designed large studies with strict exclusion of confounding factors such as smoking, hypertension and diabetes. We suggest that obesity should be carefully accounted for in any association studied in subjects with OSA.

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