The Relationship Between Sleep-Disordered Breathing and High-Sensitivity C-Reactive Protein in Japanese Men

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Study Objectives: Elevated C-reactive protein (CRP), an inflammatory marker and emerging risk factor for atherosclerosis and coronary heart disease, has been reported in overweight patients with sleep-disordered breathing (SDB). However, the contribution of C-reactive protein to this disease among non-overweight individuals is uncertain. We thus examined the relationship between serum C-reactive protein levels and nocturnal arterial oxygen desaturation, stratified by category of body mass index (BMI).

Design: Cross-sectional study.

Participants: Subjects were 316 men with a mean BMI of 25.4 kg/m^2, aged 20-79 years, who attended a sleep clinic at Osaka, Japan.

Measurements and Results: SDB was assessed by oxygen desaturation index (ODI) measured by pulse oximetry during sleep. We used 3% oxygen desaturations per hour (3% ODI), as the indicator of SDB. We also measured serum levels of C-reactive protein (CRP). After adjustment for age, BMI, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, alcohol consumption, and daily sleep duration, mean high-sensitivity CRP levels were 0.63, 0.65, and 0.96 mg/L for SDB severity levels of 3%ODI<5, 5 to 19.9, and >=20, respectively (p for trend=0.015). This association with SDB tended to be stronger in non-overweight men (BMI<25 kg/m^2) (0.47, 0.48 and 1.02 mg/L , p for trend=0.017) than in overweight men (BMI≥25 kg/m^2) (0.92, 0.87 and 1.21 mg/L , p for trend=0.11).

Conclusion: SDB is associated with increased levels of CRP, especially in non-overweight men. Our results suggest the importance of follow-up and control of SDB in the prevention of cardiovascular disease even in non-overweight SDB patients.

Keywords: Obstructive sleep apnoea, obesity, CRP, pulse oximetry

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INTRODUCTION

SLEEP-DISORDERED BREATHING (SDB), WHICH INCLUDES OBSTRUCTIVE SLEEP APNEA (OSA), IS CHARACTERIZED BY REPETITIVE EVENTS OF UPPER-AIRWAY obstruction during sleep, resulting in cessation of normal breathing, hypoxemia, and sleep fragmentation. SDB is reported to be associated with hypertension,[1,2] atherosclerosis,[3] and stroke,[4] which are probably due to sympathetic activation[5] and endothelial dysfunction.[6-8] These pathologic processes may cause inflammatory changes within the microvasculature and increase the risk of cardiovascular morbidities.

C-reactive protein (CRP), a sensitive marker of underlying systemic inflammation, has been identified as one of the risk factors of future cardiovascular disease,[9-11] although CRP levels vary among patients of different ethnic backgrounds.[12] In addition, recent studies have suggested that CRP itself may contribute to the development of atherosclerosis through leukocyte activation and endothelial dysfunction.[13-16] CRP has also been recognized to be independently associated with insulin resistance.[17-19]

Recent studies have reported elevated plasma levels of CRP in patients with OSA[20] and that treatment with nasal continuous positive airway pressure results in a reduction of CRP levels.[21] These results suggest that SDB leads to inflammatory responses that promote cardiovascular complications. However, CRP levels are elevated in obese patients,[9,22] and adiposity, in particular visceral adipose tissue, is a key promoter of low-grade chronic inflammation.[23] Studies have shown that patients with OSA have a greater amount of visceral fat, compared with obese control subjects,[24] and have higher plasma concentrations of tumor necrosis factor-α and interleukin (IL)-6 than do nonapneic obese men.[24,25] In 2 recent studies,[20,21] patients with OSA were described as obese (mean body mass index [BMI][20] = 36 kg/m^2 and mean BMI[21] = 32 kg/m^2). Therefore, it is difficult to dissociate the effect of obesity from that of OSA on CRP levels, since the above studies examined only obese patients. Recently, Guilleminault et al[26] reported no significant association between CRP and SDB among leaner subjects (mean BMI= 27.6 kg/m^2); however, they did not adjust the effect of smoking status. The relations between SDB and CRP among children have also been inconsistent.[27-29]

The aim of the present study was to confirm the association between high-sensitivity CRP (hs-CRP) and SDB in a large number of nonoverweight subjects. Specifically, we determined the relationship between nocturnal desaturation, which is often used to assess SDB, and hs-CRP levels in total, overweight, and nonoverweight subjects.

METHODS

Subjects

We studied 344 consecutive men aged between 20 and 79 years

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This was not an industry supported study. Drs. Yao, Tachibana, Okura, Ikeda, Tanigawa, Yamagishi, Sato, Shimamoto, and Iso have indicated no financial conflicts of interest.

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who attended the sleep clinic of the Osaka Medical Center for Health Science and Promotion, Osaka, Japan, between June 2002 and October 2004. Twenty-eight patients were excluded from the analysis because of unreliable data from pulse oximetry (n = 4); a prior history of ischemic heart disease (n = 9), cerebrovascular disease (n = 9), or inflammatory disease (n = 1); massive tonsillar hypertrophy (n = 2); hypothyroidism (n = 1); hyperthyroidism (n = 1); and being Caucasian (n = 1). None of the subjects had previously used nasal continuous positive airway pressure. All subjects were assessed for tonsillar hypertrophy as part of the physical examination.

Cardiovascular Risk Factors

Subjects completed a self-administrated questionnaire on smoking status, alcohol consumption, and daily sleep duration. Subjects were categorized as current smokers, exsmokers, or never smokers for smoking status and as current drinker, former drinker, or never drinker for alcohol-consumption category. Height in bare feet and weight in light clothing were measured in our clinic. BMI was calculated as weight (kg) divided by the square of the height (m^2). Arterial blood pressure was measured by trained technicians using standard mercury sphygmomanometers on the right arm of seated participants after a 5-minute rest. Hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg and/or current use of antihypertensive medications. Diabetes mellitus was defined as a fasting glucose concentration ≥ 126 mg/dL or nonfasting glucose concentration ≥ 200 mg/dL and/or current antidiabetic therapy. Hypercholesterolemia was defined as total cholesterol ≥ 220 mg/dL and/or current use of medication to treat hyperlipidemia.

Laboratory Measurements

Serum total cholesterol, low-density lipoprotein, high-density lipoprotein, glycosylated hemoglobin A1c, and blood glucose were measured by an auto analyzer (model AU2700, Olympus Optical, Tokyo, Japan). Serum lipids were measured at the laboratory of Osaka Medical Center for Health-Science and Promotion, which has been successfully standardized by WHO/CDC-NHLBI Lipid Standardization Program since 1975.[30] Serum levels of hs-CRP were determined by latex particle-enhanced immunonephelometric assay (Dade Behring Inc., IL), which was standardized by an hs-CRP survey program provided by CDC.[31]

Pulse Oximetry

All subjects were instructed to use a wristwatch-type pulse oximeter (PULSOX-3Si, Minolta Co., Osaka, Japan) at home when they were in bed on 2 separate nights. The sensor probe was fitted by the patient to the index finger and secured with surgical tape. The internal memory of the oximeter stores the values of arterial blood oxygen saturation by performing a moving average for the last 5 seconds, with updates every second; this sampling time is short enough to avoid the underestimation of oxygen desaturation.[32] We used the number of oxygen desaturation per hour (oxygen desaturation index [ODI]), as the indicator of SDB. The 3% ODI was selected as an index of oxygen desaturation, representing the number of events per hour of recording time in which blood oxygen fell by 3% or more. The higher 3% ODI on either of the 2 nights of recording was used for analysis. To minimize potential overestimation of sleep duration, subjects completed a sleep diary on these 2 nights to exclude waking time from the analysis. Four subjects (previously described) were excluded from the analysis because the recording duration per night was less than 3 hours.

The severity of SDB was categorized as unaffected (3% ODI, < 5), mild to moderate (3% ODI, ≥ 5 but < 20), and severe (3% ODI, ≥ 20). The validity of the pulse oximetry was confirmed by synchronous overnight recording of both PULSOX-3Si and standard polysomnography in 256 consecutive patients[33]: the Pearson correlation coefficient between the 3% ODI and the apnea-hypopnea index was 0.94 ($p < .001$). The sensitivity is 80% and the specificity is 95% for detecting an apnea-hypopnea index ≥ 5 by polysomnography using a cut-off threshold of 3% ODI = 5.[33]

Data Analysis

Values of hs-CRP were transformed into logarithms because of the skewed distribution. To examine relationships of variables with hs-CRP, we used a linear regression analysis with a forward-selection stepwise procedure ($p < .15$ as included). We also performed this analysis separately among nonoverweight and overweight subjects (median BMI: < 25.0 and ≥ 25.0 kg/m^2, respectively). Then, we divided the BMI into tertiles separately among nonoverweight and overweight subjects (number in each BMI category were as follows: < 21.8 kg/m^2, n = 52; 21.9-23.7 kg/m^2, n = 59; 23.8-24.9 kg/m^2, n = 53; 25.0-26.3 kg/m^2, n = 50; 26.4-28.5 kg/m^2, n = 52; and > 28.6 kg/m^2; n = 50). We calculated age-adjusted and multivariate-adjusted (age, BMI category, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, alcohol consumption, and daily sleep duration) mean values of hs-CRP according to the subgroups of 3% ODI < 5, 5 to 19.9, and ≥ 20. The difference of mean hs-CRP levels was examined by the Dunnett multiple-comparison method, using a subgroup of 3% ODI < 5 as the reference. Odds ratios (OR) of a hs-CRP ≥ 1.0 mg/L were also calculated according to ODI levels (3% ODI < 20 and ≥ 20) for total, nonoverweight, and overweight subjects. A linear trend of 3% ODI levels with hs-CRP levels was tested using median values of the 3% ODI categories. The significance for the interaction between BMI and 3% ODI was tested using the cross-product terms of these variables. All statistical tests were 2 tailed and conducted using SAS software, version 8.02 (SAS Inc, Cary, NC).[34] A p value less than .05 denoted the presence of a statistically significant difference.

RESULTS

The mean age of all subjects was 49.6 years, and the mean 3% ODI was 15.0. The percentages of 3% ODI < 5, 5 to 19.9, and ≥ 20 were 28%, 46%, and 26%, respectively. For nonoverweight men, the mean age was 49.0 years, and the mean 3% ODI was 8.9. For overweight men, the mean age was 50.2 years, and the mean 3% ODI was 21.6. Other demographic data are presented in Table 1. The regression model for hs-CRP (n = 316, model $R^2 = 0.19$, $F = 11.2$, $p < .001$) identified BMI (partial R^2=0.14, $p < .001$), 3% ODI (partial $R^2 = 0.02$, $p = .01$), and current smoking (partial $R^2 = 0.02$, $p = .01$) as significant determinants. For nonoverweight men (BMI < 25.0 kg/m^2), the significant predictors for hs-CRP levels were 3% ODI (partial $R^2 = 0.08$, $p = .004$) but not age (partial $R^2 = 0.02$, $p = .06$), current smoking (partial $R^2 = 0.01$, $p = .12$), or BMI (partial $R^2 = 0.01$, $p = .10$). For overweight men (BMI ≥ 25.0 kg/m^2), the significant predictors for hs-CRP

Table 1—Characteristics of Subjects

	All subjects	BMI < 25.0 kg/m²	BMI ≥ 25.0 kg/m²
No.	316	164	152
3% oxygen desaturations	15.0 ± 16.4	8.9 ± 8.7	21.6 ± 20.0***
3% ODI category , no. (%)			
< 5	90 (28.5)	65 (39.6)	25 (16.4)
5-19.9	144 (45.6)	80 (48.8)	64 (42.1)
≥ 20	82 (25.9)	19 (11.6)	63 (41.4)
BMI, kg/m²	25.4 ± 3.9	22.6 ± 1.7	28.4 ± 3.3***
Age, y	49.6 ± 13.0	49.0 ± 13.2	50.2 ± 12.8
hs-CRP, mg/dL[a]	0.71 (0.08-6.43)	0.52 (0.06-4.59)	1.00 (0.13-7.60)***
hs-CRP ≥ 1.0, %	34.5	23.2	46.7***
WBC, 10²/mm²	63.1 ± 15.5	59.8 ± 14.4	66.6 ± 16.0***
LDL, mg/dL	124.8 ± 31.5	122.1 ± 28.9	127.7 ± 33.9
HDL, mg/dL	52.0 ± 13.7	56.2 ± 15.1	47.6 ± 10.2***
Blood pressure, mm Hg			
Systolic	126.3 ± 16.9	122.1 ± 15.6	130.9 ± 17.0***
Diastolic	76.1 ± 13.2	73.2 ± 12.9	79.1 ± 12.8***
Disease presence, no. (%)			
Hypertension	103 (32.6)	41 (25.0)	62 (40.8)***
Hypercholesterolemia	105 (33.2)	47 (28.7)	58 (38.2)
Diabetes mellitus	17 (5.4)	6 (3.7)	11 (7.2)
Smoking status, no. (%)			
Current	89 (28.2)	41 (25.0)	48 (31.6)
Former	127 (40.2)	71 (43.3)	56 (36.8)
Never	100 (31.7)	52 (31.7)	48 (31.6)
Drinking status, no. (%)			
Current	213 (67.4)	110 (67.0)	103 (67.8)
Former	17 (5.4)	7 (4.3)	10 (6.6)
Never	86 (27.2)	47 (28.7)	39 (25.7)
Daily sleep duration, h/day	6.3±1.2	6.4±1.2	6.3±1.2

Data are mean ± SD unless otherwise indicated. ODI refers to oxygen desaturation index; WBC, white blood cell count; LDL, low-density lipoprotein; HDL, high-density lipoprotein.
[a]High-sensitivity C-reactive protein (hs-CRP) value is expressed as geometric mean (95% confidence interval).
*p < .05, **p < .01, ***p < .001, compared with subjects with body mass index (BMI) < 25.0 kg/m²

levels were BMI (partial $R^2 = 0.08$, $p < .001$) and current smoking (partial $R^2 = 0.03$, $p = .04$) but not 3% ODI (partial $R^2 = 0.02$, $p = .07$).

Table 2 shows the mean values (95% confidence interval [CI], mg/L) of hs-CRP according to ODI. For total subjects, the mean value of hs-CRP was positively associated with 3% ODI, even after adjustment for age, BMI, hypertension, diabetes mellitus, hypercholesterolemia, smoking status, alcohol consumption, and daily sleep duration (p for trend = .015). Age-adjusted and multivariate-adjusted mean values of hs-CRP were significantly higher in the severe-SDB group (3% ODI ≥ 20) than in the unaffected group (< 5). These differences were more evident for nonoverweight men than for overweight men, although the interaction did not reach statistical significance (p = .30). Mean hs-CRP levels did not vary between the group with mild to moderate SDB (3% ODI: 5-19.9) and the unaffected group.

Multivariate-adjusted OR of hs-CRP ≥ 1.0 mg/L for 3% ODI ≥ 20 vs < 20 was 2.1 (CI: 1.1-4.0) for total subjects, 4.3 (CI: 1.4-13.9) for nonoverweight subjects, and 2.1 (CI: 1.0-4.9) for overweight subjects (not shown in the table). These relationships did not change even after we repeated the analysis with glycosylated hemoglobin A1c concentration as an indicator of diabetes mellitus.

Table 2—Adjusted Values of hs-CRP According to 3% ODI Levels

BMI category	3% ODI category			p for trend
	< 5	5-19.9	≥ 20	
All subjects				
No.	90	144	82	
hs-CRP, mg/dL				
Age adjusted	0.55 (0.44-0.68)	0.63 (0.53-0.75)	1.19 (0.94-1.51)***	< .001
Multivariate adjusted[a]	0.63 (0.50-0.79)	0.65(0.55-0.77)	0.96 (0.74-1.24)*	.015
BMI < 25.0 kg/m²				
No.	65	80	19	
hs-CRP, mg/dL				
Age adjusted	0.46 (0.36-0.60)	0.48 (0.38-0.60)	1.14 (0.71-1.85)**	.002
Multivariate adjusted[a]	0.47 (0.36-0.62)	0.48 (0.38-0.61)	1.02 (0.60-1.72)*	.017
BMI ≥ 25.0 kg/m²				
No.	25	64	63	
hs-CRP, mg/dL				
Age adjusted	0.88 (0.59-1.32)	0.87 (0.68-1.11)	1.23 (0.95-1.58)	.049
Multivariate adjusted[a]	0.92 (0.60-1.39)	0.87 (0.67-1.12)	1.21 (0.93-1.58)	.109

Values of high-sensitivity C-reactive protein (hs-CRP) are presented as mean (confidence interval).
[a]Adjusted for age, body mass index (BMI) (6 categories), hypertension, hypercholesterolemia, diabetes mellitus, alcohol consumption, smoking status, and sleep duration.
*p < .05, **p < .01, ***p < .001, for difference, compared with 3% oxygen desaturation index (ODI) < 5, according to the Dunnett multiple-comparison method.

DISCUSSION

We found a significant positive association between CRP levels and the severity of SDB among Japanese men, independent of age, BMI, hypertension, hypercholesterolemia, diabetes mellitus, smoking status, alcohol consumption, and daily sleep duration. The present study confirmed the association between hs-CRP and SDB with large samples, including nonoverweight subjects. Moreover, we found the association with SDB tended to be stronger in nonoverweight subjects than in overweight subjects. One possible explanation for the difference between nonoverweight and overweight subjects is a masking for the association by a strong effect of being overweight on the hs-CRP and SDB.

Mean hs-CRP levels did not differ between the group with mild to moderate SDB and the unaffected group. This result suggests a threshold on the relationships between SDB severity and hs-CRP, as has been shown in a previous report.[29]

CRP, which has been recognized as a sensitive inflammatory marker, is one of the acute-phase proteins derived from the liver and largely induced by IL-6. [35] Unlike cytokines, CRP levels are quite stable in the same individual, with an absence of diurnal variation in healthy subjects.[36] Ongoing inflammatory responses

may play important roles in athelosclerosis.[37] A Japanese follow-up study has shown that increased hs-CRP levels are associated with the development of carotid atherosclerosis.[38] Furthermore, recent epidemiologic studies have shown that high levels of CRP predict cardiovascular events.[9,22,39,40] Ridker et al[41] reported that patients with CRP levels lower than 1 mg/L had the lowest risk, those with levels between 1 and 3 mg/L faced intermediate risk, and those with levels above 3 mg/L were at highest risk of cardiovascular events. This implies that half of our subjects with 3% ODI $\geq$ 20 may have an intermediate risk of cardiovascular disease, since the mean hs-CRP was about 1 mg/L.

The early steps of atherogenesis involve the elicitation of proinflammatory cytokines, causing hepatic production of CRP. However, the precise mechanism responsible for the elevation of cytokines and hs-CRP among patients with SDB is unknown at present. Possible mechanisms for the link between SDB and elevated CRP levels may include repetitive hypoxemia and sleep deprivation. In this regard, hypoxemia of high altitude induces IL-6 and CRP in normal humans.[42] Repetitive apnea, which induces intermittent hypoxia, may lead to elevation of IL-6 and hs-CRP because hypoxia modulates the expression of several endothelial genes, including those for vascular endothelial growth factor, endothelin-1, and platelet-derived growth factor.[43,44] Recently, Yokoe et al reported that a 1-month treatment with nasal continuous positive airway pressure significantly reduces plasma levels of both IL-6 and CRP without any changes in BMI.[21]

An epidemiologic survey indicates that short sleep duration is associated with cardiovascular morbidity.[45] In addition, a recent experimental study revealed that both acute total and short-term partial sleep deprivation resulted in elevation of hs-CRP concentrations in healthy adult subjects.[46] Based on this background information, we adjusted for the self-reported daily sleep duration in the multivariate analysis, but such adjustment did not change the results.

One limitation of the present study is the use of pulse oximetry rather than polysomnography. The potential disadvantage of pulse oximetry is the underestimation of respiratory disturbance events during sleep, particularly among nonoverweight individuals. The reason for the lower sensitivity of pulse oximetry in lean subjects is considered to be due to sufficient functional reserve of lung volume to maintain normal blood oxygen level, along with difficulty in detecting hypopneic events that did not cause oxygen desaturation. However, in the present study, the association between CRP and SDB was more evident among nonoverweight subjects, in spite of the potential dilution effect.

The second limitation is that the total sleep duration was based on self-reporting and recording time; however, only polysomnography provides the real sleep time. The sleep time estimated by pulse oximetry could be longer than true total sleep time, which leads to an underestimation of 3% ODI. This disadvantage may weaken the association between SDB and CRP, and, therefore, the real association would be stronger than our results. On the other hand, the advantage of pulse oximetry is reduced readers' bias and reflects only significant desaturation, whereas the scoring variability of polysomnography between technologists is often large.[47] Thus, in examining the association between CRP and SDB, there is no evidence about which index is more meaningful between apnea-hypopnea index and ODI.

The third limitation was that we excluded female subjects because of the small number available. However, SDB is more common in men than in women, and very little is known about sex differences in the pathogenesis of this disorder.

Finally, there would be residual confounding of the association between CRP and SDB. Although we adjusted for various risk factors for CRP, we cannot exclude the possible influence of other risk factors, especially adiposity. However, adiposity is not a serious problem in Japanese men compared to Westerners.[48] Therefore, although we could not obtain information on adiposity, it is unlikely that adiposity strongly confounded the association in our study.

It is possible that the use of hypolipidemic agents by a subgroup of our patients might have affected our results because the pravastatin inflammation/CRP evaluation study demonstrated that pravastatin reduces CRP concentrations through the anti-inflammatory effects of the statin.[49] However, the results did not change after exclusion of data from patients treated with statins.

In conclusion, we found a significant positive association between CRP levels and the severity of SDB among Japanese men, and this association was more evident in nonoverweight than in overweight individuals. These findings suggest the importance of follow-up and control of SDB, even for nonoverweight individuals, in the prevention of cardiovascular disease.

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