ORIGINAL ARTICLE

CRP and Metabolic Syndrome in Obstructive Sleep Apnea

Babak Amra, Hematollah Babaie, Mohammad Golshan
Isfahan University of Medical Sciences, Isfahan, Iran

Indian J Sleep Med 2007; 2.1, 28-31

Introduction

Obstructive sleep apnea syndrome (OSAS) is frequently associated with some atherosclerotic risk factors, such as hypertension, abnormal glucose metabolism, and obesity, and with increased cardiovascular morbidity and mortality (1–4). These risk factors are components of the metabolic syndrome, which has also been shown to be associated with an increased risk of atherosclerotic cardiovascular morbidity and mortality (5–7).

With respect to previous studies the metabolic syndrome frequently occurs in association with OSAS (8, 9) . On the other hand Inflammation plays a key role in the progression of atherosclerosis (10), and the plasma level of C-reactive protein (CRP) has also been noted as a marker of atherosclerotic cardiovascular events (11, 12). While this marker have been shown to be elevated in both subjects with OSAS (13) and those with the metabolic syndrome (14), a few studies have been conducted to determine whether the concurrent presence of metabolic syndrome and OSAS is associated with any other additive elevation cardiovascular risk markers (15). Therefore, the present cross-sectional study was conducted in subjects attending a sleep clinic in which the subjects were examined to determine whether the plasma levels of CRP were elevated in the presence of OSAS with or without metabolic syndrome, and also to determine if the concurrent presence of the metabolic syndrome was associated with exacerbation of the increase in plasma levels of CRP in subjects with OSAS.

Address for Correspondence
Dr. Babak Amra
Bamdad Building , Sheikh Mofid
Isfahan- Iran
Fax:+98 311 6623967
Email: amra@med.mui.ac.ir

Methods

Subjects

Fifty consecutive subjects (33 male and 17 female; age, 54.2±14.9 years old), who had obstructive sleep apnea which was diagnosed in the Bamdad Respiratory Research center, between September 2006 and March 2007 were enrolled in this study. All of the participants were admitted to sleep clinic for sleep diagnostic assessments, blood examinations under fasting conditions. Informed consent was obtained from all participants, the protocol was approved by the Isfahan University of Medical Sciences ethics committee. ≥None of the patients were diagnosed as having central apnea.

Definitions

We used the modified National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III; ATP III) criteria (16) for detection of the metabolic syndrome: high-density lipoprotein cholesterol <40mg/dl (male) and <50 mg/dl (female); triglycerides ≥150 mg/dl; blood pressure 130/85 mmHg or current use of antihypertensive drugs; fasting glucose 110mg/dl; and waist circumference was>102centimeter)

Nocturnal Sleep Studies

All the subjects underwent polysomnography (Embella; Res Med, Netherland) in a Bamdad sleep laboratory.

Electroencephalography, electro-oculography, electromyography, and electrocardiography were performed simultaneously and visually scored according to standard criteria (17). Ventilatory flow at the nose and mouth was measured with thermistors. The arterial oxygen saturation

was measured transcutaneously at the fingertip by pulse oximetry .Apnea was defined as a continuous cessation of airflow for more than 10 s, and hypopnea was defined as a 50% reduction in airflow for more than 10 s with an oxygen desaturation of 4% and a reduction in chest wall movement (18). The apnea hypopnea index (AHI) was calculated as the total number of episodes of apnea and hypopnea per hour of sleep. An AHI 5 was considered diagnostic for OSAS.

Blood pressure wasmeasured using a usingan Omron automatic oscillometric digital blood pressure monitor (HEM-705CP, Omron Corporation, Tokyo, Japan).

Circulating parameters assay

All subjects had fasting blood samples taken between 07:00 AM and 08:00 AM. Blood samples were immediately sent to the hospital laboratory for estimation of lipid levels. Cholesterol and triglyceride concentrations in serum and lipoprotein fractions were determined enzymatically using standard laboratory procedures. Serum levels of CRP were measured with a latex particle-enhanced immunoturbidimetric assay. The normal range for CRP levels was considered to be 0 to 5 mg/L.

Statistical Analysis

The mean and standard error of the mean (SEM) values were determined for continuous variables and percentage for categorical variables. The significance of differences within groups was analyzed using the Student t test. Correlations were analyzed with the Pearson correlation coefficient. To assess the relative strength of the association of OSAS as well as possible confounding factors with CRP, we employed multiple regression analysis for the patients with OSAS as a single group. In this analysis, serum levels of CRP were used as a dependent variable and the order of inclusion in the model of the following independent variables was evaluated: AHI, BMI, triglyceride, HDL, fasting blood sugar, waist circumference, systolic blood pressure and diastolic blood pressure.

All statistical analyses were carried out using statistical software (SPSS, version 13.0 for Windows; SPSS Inc; Chicago, IL). Differences were considered significant at P < 0.05.

Results

After subjects underwent PSG, 50 were considered to have OSAS, including 31 patients with metabolic syndrome and 19 patients without metabolic syndrome. The demographic and clinical data of the two groups are presented in the Table. The serum CRP levels were significantly elevated in the OSAS + metabolic syndrome group compared to the other group ($P < 0.05$) (Table).

Evaluation of the association between the serum CRP level and severity of OSAS revealed that CRP levels were not correlated with AHI in OSAS

Evaluation of the relative strength of association using multiple regression analysis between CRP and OSAS severity (AHI) as well as the other possible confounding variables (FBS, HDL, fasting glucose, waist circumference, blood pressure, triglycerides) showed that CRP levels were not associated with AHI in both the OSAS + metabolic syndrome and OSAS without metabolic syndrome.

Table 1 : Demographic and Clinical Data of the Three Study Groups

Patient Characteristic	OSAS with Metabolic Syndrome	OSAS without Metabolic Syndrome	P value
Number of subjects	31	19	
Age (years)	56.2±16	51±13	0.11
Gender male/female)	16/15	17/2	
SBP (mmHg)	148±23	135±20	0.03
DBP(mmHg)	97±14	87±12	0.04
TG (mg/l)	189±61	139±18	0.00
HDL cholesterol (mmol/l)	35	42	0.00
FBS (mmol/l)	98±22	88±15	0.00
Waist circumference(cm)	110±15	100±14	0.08
CRP(mg/l)	6.8±8.1	3.4±0.3	0.03

SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; TG, triglycerides; FBS, fasting blood sugar;

Discussion

This cross-sectional study demonstrated that OSAS with metabolic syndrome was associated with elevation in the plasma levels of CRP, and that the concurrent presence of the metabolic syndrome in subjects with OSAS was associated with the elevations of the plasma levels of CRP.

In patients with the metabolic syndrome, in addition to the cardiovascular risk factors that comprise the metabolic syndrome (obesity, insulin resistance, dyslipidemia, and the

elevation of blood pressure), inflammation, oxidative stress, sympathetic activation, and hemostatic and fibrinolytic abnormalities are thought to act as atherogenic factors (19). Inflammation is thought to play a major role in most of these effects, which are frequently encountered in subjects with OSAS (8). In the present study, the plasma levels of CRP were higher in subjects with OSAS and the concurrent presence of the metabolic syndrome. CRP is thought to be a marker of systemic inflammation related to atherosclerosis (20). Furthermore, recent studies have demonstrated that CRP acts as a direct atherogenic factor (21). Thus, our results suggest that the concurrent presence of metabolic syndrome in subjects with OSAS also exacerbates the cardiovascular risk as reflected by the plasma CRP levels. The atherosclerotic risk factors comprising the metabolic syndrome are frequently encountered in subjects with OSAS. Recently, Coughlin et al. demonstrated that OSAS was independently associated with an increase in cardiovascular risk factors that comprise the metabolic syndrome (9).

However, whether the elevated cardiovascular risk in subjects with OSAS is due to the coexistence of components of the metabolic syndrome, or represents effects specific to OSAS remains to be evaluated. In subjects with the metabolic syndrome, elevated plasma levels of CRP have been reported to provide additional prognostic information for cardiovascular events (22); thus, plasma CRP is thought to be an additive risk in global cardiovascular risk prediction in subjects with the metabolic syndrome.

These results raise an important issue, namely, whether the concurrent presence of OSAS in subjects with the metabolic syndrome may also contribute to the prognosis in subjects with the metabolic syndrome— that is, whether OSAS is also an additive cardiovascular risk factor in subjects with the metabolic syndrome. However, the subjects of this study comprised a specific group consisting of subjects visiting a sleep clinic, and thus further studies will be needed to clarify this issue in a general cohort that also includes subjects with the metabolic syndrome. The present study had some limitations. This was a cross-sectional study and only demonstrated the worsening of surrogate markers of the prognosis in subjects with OSAS who also satisfied the criteria of metabolic syndrome.

Some studies have de monstrated that central obesity, rather than body mass index, may be more closely related to arterial stiffness and the plasma levels of CRP (24). Therefore, the significance of central obesity as a determinant of plasma level of CRP should be evaluated in future studies.

The present study did not deal with the precise mechanisms underlying the exacerbation of elevated plasma levels of CRP in the concurrent presence of the metabolic syndrome in subjects with OSAS.

In conclusion, the present study demonstrated plasma levels of CRP in subjects with OSAS and, furthermore, that the concurrent presence of the metabolic syndrome in subjects augmented this elevation of plasma levels of CRP in subjects with OSAS. The concurrent presence of the metabolic syndrome in subjects with OSAS may exacerbate the cardiovascular risk reflected by increased arterial stiffness, and increased body mass index, which is a component of the metabolic syndrome, may exacerbate the cardiovascular risk related to an increased plasma level of CRP. Therefore, the concurrent presence of the metabolic syndrome may constitute an additive cardiovascular risk factor in subjects with OSAS. Thus, examination to detect the concurrent presence of the metabolic syndrome is warranted in the management of patients with OSAS.

References

1. **Mooe T**, Franklin KA, Holmstrom K, Rabben T, Wiklund U:Sleep-disordered breathing and coronary artery disease: long term prognosis. *Am J Respir Crit Care Med 2001; 164: 1910–1913.*
2. **Milleron O**, Pilliere R, Foucher A, et al: Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study. *Eur Heart J 2004; 25: 728–734.*
3. **Shepertycky MR,** Al-Barrak M, Kryger MH: Mobidity and mortality in obstructive sleep apnea syndrome 1: effect of treatment on cardiovascular morbidity. *Sleep Biol Rhythms 2003; 1: 15–28.*
4. **Budhiraja R,** Sharief I, Quan SF: Sleep disordered breathing and hypertension. J *Clin Sleep Med 2005; 1: 401–404.*
5. **Lakka HM**, Laaksonen DE, Lakka TA, et al: The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. *JAMA 2002; 288: 2709–2716.*
6. **Malik S**, Wong ND, Franklin SS, et al: Impact of the metabolic syndrome on mortality from coronary heart disease, cardiovascular disease, and all causes in United States adults. *Circulation 2004; 101: 1239–1244.*
7. **Takeuchi H**, Saitoh S, Takagi S, et al: Metabolic syndrome and cardiac disease in Japanese men: applicability of the concept of metabolic syndrome defined by the National Cholesterol Education Program"Adult Treatment Panel III to Japanese men¯#the Tanno and Sobetsu Study. *Hypertens Res 2005; 28: 203–208.*
8. **Wolk R**, Shamsuzzaman AS, Somers VK: Obesity, sleep apnea, and hypertension. *Hypertension 2003; 42: 1067–1074.*
9. **Coughlin SR**, Mawdsley L, Mugarza JA, Calverley PM,

Wilding JP: Obstructive sleep apnoea is independently associated with an increased prevalence of metabolic syndrome. *Eur Heart J 2004; 25: 735–741.*

10. **Glass CK**, Witztum JL: Atherosclerosis. The road ahead. *Cell 2001; 104: 503–516.*
11. **Ridker PM,** Brown NJ, Vaughan DE, Harrison DG, Mehta JL: Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. *Circulation 2004; 109 (Suppl 1): IV6–IV19.*
12. **Danesh J,** Wheeler JG, Hirschfield GM, et al: C-reactive protein and other circulating markers of inflammation in the prediction of coronary heart disease. *N Engl J Med 2004;350: 1387–1397.*
13. **Shamsuzzaman AS**, Winnicki M, Lanfranchi P, et al: Elevated C-reactive protein in patients with obstructive sleep apnea. *Circulation 2002; 105: 2462–2464.*
14. **Festa A**, D'Agostino R Jr, Howard G, Mykkanen L, Tracy RP, Haffner SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). *Circulation 2000; 102: 42–47.*
15. **McArdle N**, Hillman D, Beilin L, Watts G: Metabolic risk factors for vascular disease in obstructive sleep apnea: A matched controlled study. *Am J Respir Crit Care Med 2007;175 : 190-195*
16. Executive summary of the third report of The National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III). *JAMA 2001; **285**(19):2486–2497.*
17. **Rechtshaffen A**, Kales A (eds): A Manual of Standardized Terminology: Techniques and Scoring System for Sleep Stages of Human Subjects. Los Angeles, UCLA Brain Information Service/Brain Research Institute, 1968.
18. American Academy of Sleep Medicine Task Force: Sleep related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep 1999; 22: 667–689.*
19. **Doelle GC:** The clinical picture of metabolic syndrome. An update on this complex of conditions and risk factors. *Postgrad Med 2004; 116: 30–38.*
20. **Jialal I**, Devaraj S, Venugopal SK: C-reactive protein: risk marker or mediator in atherothrombosis? *Hypertension 2004; 44: 6–11.*
21. **Calabro P,** Willerson JT, Yeh ET: Inflammatory cytokines stimulated C-reactive protein production by human coronary artery smooth muscle cells. *Circulation 2003; 108:1930–1932.*
22. **Sattar N**, Gaw A, Scherbakova O, et al: Metabolic syndrome with and without C-reactive protein as a predictor of coronary heart disease and diabetes in the West of Scotland Coronary Prevention Study. *Circulation 2003; 108: 414–419.*
23. **Pannacciulli N**, Cantatore FP, Minenna A, Bellacicco M, Giorgino R, De Pergola G: C-reactive protein is independently associated with total body fat, central fat, and insulin resistance in adult women. *Int J Obes Relat Metab Disord 2001; 25: 1416–1420.*