Biomarkers, 2012; 17(3): 248–253

ISSN 1354-750X print/ISSN 1366-5804 online
DOI: 10.3109/1354750X.2012.658864

informa
healthcare

RESEARCH ARTICLE

Elevated levels of serum chemerin in patients with obstructive sleep apnea syndrome

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Abstract

Context: Chemerin is implicated to be correlated with obesity and inflammation.

Objective: This study aims to investigate whether serum chemerin is associated with the presence of obstructive sleep apnea syndrome (OSAS).

Methods: A total of 132 patients with OSAS and 108 healthy subjects were enrolled in this study.

Results: Serum chemerin levels were significantly elevated in OSAS patients (120.93 ± 25.84 μg/L vs. 107.51 ± 20.41 μg/L). Multivariable logistic regression analysis revealed that serum chemerin levels were an independent determinant of the presence of OSAS (OR 1.030, 95% CI 1.016–1.045; $p < 0.001$). Serum chemerin levels in severe OSAS patients were significantly higher compared with those in mild and moderate OSAS patients ($p = 0.015$ and $p = 0.020$, respectively). Spearman correlation analysis indicated that serum chemerin levels were correlated with the severity of OSAS ($r = 0.210$, $p = 0.016$). Serum chemerin were positively correlated with waist circumference ($r = 0.164$, $p = 0.008$), body mass index ($r = 0.158$, $p = 0.014$), systolic blood pressure ($r = 0.135$, $p = 0.037$), homeostasis model assessment of insulin resistance ($r = 0.140$, $p = 0.031$), C-reactive protein ($r = 0.202$, $p = 0.002$), and apnea–hypopnea index ($r = 0.152$, $p = 0.022$).

Conclusion: Elevated serum chemerin levels could be an independent predicting marker of the presence and severity of OSAS.

Keywords: Chemerin, obstructive sleep apnea syndrome, obesity, inflammation

Introduction

Obstructive sleep apnea syndrome (OSAS) is a chronic condition characterized by repetitive episodes of upper airway collapse during sleep, leading to oxygen desaturation, fragmented sleep, and daytime somnolence (Deegan & McNicholas 1995). Approximately 3–7% of adult men and 2–5% of adult women are estimated to be affected by OSAS (Punjabi et al. 2008). Obesity is a major risk factor for OSAS and approximately 70% of OSAS patients are obese (Malhotra et al. 2002). Furthermore, inflammation is considered to be involved in the mechanism of OSAS. A wide variety of inflammatory markers are elevated in the circulation of patients with OSAS (Kent et al. 2011). The morbidity and mortality of OSAS is high (Madani et al. 2009). Accumulating evidence indicates that OSAS is associated with diabetes, cardiovascular diseases, and metabolic syndrome (MetS), independently of obesity (Pack et al. 2006). In addition, excessive daytime sleepiness, which is caused by OSAS, results in negative impact on the quality of life, and professional performance including vehicle and industrial accidents (Lurie et al. 2011).

Chemerin, a newly discovered adipokine, is expressed in a number of tissues including the liver, pancreas, lung, and adipose tissue (Goralski et al. 2007). It plays an important role in the differentiation of normal adipocyte and regulation of the expression of genes involved in glucose and lipid homeostasis such as glucose transporter-4 and fatty acid synthase (Roh et al. 2007). Chemerin has been demonstrated to be associated with components of MetS including obesity, dyslipidemia, insulin resistance, and

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(Received 12 December 2011; revised 13 January 2012; accepted 16 January 2012)

hypertension (Bozaoglu et al. 2007, Stejskal et al. 2008, Bozaoglu et al. 2009). In addition, recent studies indicate that chemerin is correlated with inflammation markers including high sensitivity C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor-α (Lehrke et al. 2009, Weigert et al. 2010). Obesity and inflammation are considered to be involved in the pathophysiology of OSAS. Therefore, it is hypothesized that chemerin may play a role in the mechanism of OSAS.

Although there have been studies on the association of adipokines such as adiponectin, leptin, visfatin, and apelin with OSAS, no investigation on the association between chemerin and OSAS has been performed yet. The present study aims to investigate the serum levels of chemerin in patients with OSAS in order to assess its role in pathophysiology of OSAS.

Materials and methods

Patients

A total of 132 newly diagnosed male patients with OSAS were enrolled in this study. All patients with OSAS were diagnosed with polysomnography (PSG). Patients who had personal or family history of psychiatric disorders, history of alcohol and drug abuse, systemic illnesses such as heart failure, chronic renal failure, chronic obstructive pulmonary disease were excluded. The control group consisted of 108 male healthy check-up examinees who matched to the cases by age, gender, and body mass index (BMI). PSG was also performed in the control group to exclude OSAS. Subjects with any symptoms of OSAS were excluded from the control group.

This study was approved by the ethics committee of our hospital, and informed consent was obtained from all participants.

Sleep study

Full PSG monitoring was performed in all participants using the Compumedics E-series Sleep System (Compumedics Sleep: Melbourne, Australia). Polysomnographic monitoring consisted of monitoring of sleep by electroencephalography, electrooculography, electromyography, airflow, and respiratory muscle effort, and included measures of electrocardiographic rhythm and blood oxygen saturation. Apneas were defined as complete cessation of airflow ≥ 10 sec. Hypopnea was defined as a reduction in airflow with a 50% from baseline for at least 10 seconds, a 3% drop in oxygen saturation from the preceding stable saturation, and/or arousal. Apnea–hypopnea index (AHI) was defined as the number of apneas and hypopneas per hour of sleep. Subjects with AHI <5 were included in the control group. Patients with AHI ≥5 were considered as OSAS patients. An AHI of ≥5 to <15 indicated mild OSAS, ≥15 to <30 moderate OSAS, and ≥30 severe OSAS.

Measurements

At first examinations, height, weight, waist circumference (WC), and blood pressure were measured. Venous blood was collected after a minimum of 10 h of fasting. Fasting plasma glucose, serum triglycerides (TG), serum total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), and CRP were tested using an auto biochemistry instrument (Hitachi 7170, Tokyo, Japan). Plasma fasting insulin level was tested by radioimmunoassay. Serum chemerin levels were measured by a commercially enzyme-linked immunosorbent assay (Phoenix Pharmaceuticals, Belmont, CA). Intra- and inter-assay coefficient of variations was 5–7% and 12–15%, respectively. The detection limit ranged from 0 to 100 μg/L. BMI was calculated as weight in kilograms divided by height squared in meters (kg m^{-2}). Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as insulin reading (μIU/mL) multiplied by plasma glucose level (mmol/L) and divided by 22.5.

Statistical analysis

Sample size was determined by power analysis using preliminary data obtained in our laboratory with the following assumptions: α of 0.05 (two-tailed), power of 90%, difference in serum chemerin levels between OSAS patients and healthy control of 13.5 μg/L, and a standard deviation of 24.50 μg/L. Therefore, a minimum of 71 patients with OSAS would detect a difference in serum chemerin levels (Dupont & Plummer 1990). Data are presented as means ± standard deviation (SD). Data normality was analyzed using the Kolmogorov–Smirnov test. The values were analyzed by the Student's *t*-test to compare the differences among two groups. Categorical variables were analyzed by the χ^2 tests. Univariate analysis was performed and the variables with a $p < 0.10$ were then entered into a backward stepwise multivariate logistic regression model to calculate the odds ratio values (OR) and 95% confidence intervals (CI) for the presence of OSAS. One-way ANOVA or χ^2 tests were used to compare the differences of serum chemerin levels among mild, moderate, and severe OSAS patients. The correlation between serum chemerin and other parameters were analyzed using simple linear regression analysis. Then a multiple stepwise linear regression analysis was used to determine the contribution of various factors to serum chemerin. The correlations are scored as weak ($r = 0$–0.49), moderate ($r = 0.5$–0.74), or strong ($r = 0.75$–1). As CRP, AHI, and serum chemerin levels were not normally distributed, logarithmic (log) transformed values were used for multivariate regression analysis. Statistical analysis was carried out using SPSS version 12.0 software program (SPSS Inc, Chicago, IL). Differences were considered significant at $p < 0.05$.

Results

Baseline clinical characteristics

The clinical and laboratory characteristics of OSAS patients and control subjects are presented in Table 1. OSAS patients showed higher levels of HOMA-IR and

Table 1. Clinical and biochemical characteristics of OSAS patients and healthy controls.

	Control	OSAS patients	*p* value
N	108	132	
Age (years)	47.29 ± 10.89	47.51 ± 10.31	0.872
WC (cm)	85.26 ± 9.34	85.78 ± 9.58	0.674
BMI (kg/m^2)	27.07 ± 3.10	27.17 ± 3.77	0.818
SBP (mmHg)	135.56 ± 18.71	137.05 ± 19.25	0.546
DBP (mmHg)	84.54 ± 9.99	84.92 ± 11.62	0.785
HOMA-IR	3.17 ± 0.85	3.83 ± 0.98	<0.001
TC (mmol/L)	4.76 ± 1.01	4.89 ± 1.06	0.343
TG (mmol/L)	1.59 ± 0.49	1.68 ± 0.48	0.593
LDL-C (mmol/L)	2.90 ± 0.85	3.01 ± 0.91	0.373
HDL-C (mmol/L)	1.51 ± 0.31	1.51 ± 0.27	0.933
CRP (mg/L)	2.76 ± 0.91	3.84 ± 1.25	<0.001
Chemerin (μg/L)	107.51 ± 20.41	120.93 ± 25.84	<0.001
Obesity, *n* (%)	74 (68.52%)	96 (72.73%)	0.475
Diatetes, *n* (%)	23 (21.30%)	38 (28.79%)	0.185
CAD, *n* (%)	18 (16.67%)	29 (21.97%)	0.303

BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol; OSAS, obstructive sleep apnea syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

CRP compared with healthy controls. There were no significant differences in age, WC, BMI, systolic blood pressure (SBP), diastolic blood pressure, serum TC, TG, LDL-C and HDL-C, as well as the percentages of obesity, diabetes and CAD patients between the two groups.

Serum chemerin levels in OSAS patients

Table 1 shows the serum levels of chemerin between OSAS patients and healthy controls. The level of serum chemerin was significantly elevated in OSAS patients compared with healthy controls (120.93 ± 25.84 μg/L vs. 107.51 ± 20.41 μg/L). Simple logistic regression analysis indicated that HOMA-IR (OR 1.775, 95% CI 1.344–2.345; $p < 0.001$), CRP (OR 1.302, 95% CI 1.126–1.506; $p < 0.001$), and chemerin levels (OR 1.038, 95% CI 1.021–1.054; $p < 0.001$) showed a trend ($p < 0.10$) toward an association with the presence of OSAS (Table 2). All these parameters were then entered into a multivariate logistic regression model. Chemerin levels remained to be associated with the presence of OSAS (OR 1.030, 95% CI 1.016–1.045; $p < 0.001$) (Table 2).

The chemerin levels with the severity of OSAS

The chemerin levels in mild, moderate, and severe OSAS patients are shown in Figure 1. Serum chemerin levels in severe OSAS patients were significantly higher compared with those in mild and moderate OSAS patients ($p = 0.015$ and $p = 0.020$, respectively). However, there were no differences in serum chemerin levels between mild and moderate OSAS patients ($p = 0.349$). Spearman correlation analysis indicated that serum chemerin levels were weakly correlated with the severity of OSAS ($r = 0.210$, $p = 0.016$).

Table 2. Logistic regression analysis for the presence of OSAS.

	Simple regression		Multiple regression	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age (years)	0.995 (0.967–1.024)	0.718		
WC (cm)	0.999 (0.968–1.032)	0.975		
BMI (kg/m^2)	1.020 (0.930–1.118)	0.674		
SBP (mmHg)	1.006 (0.983–1.029)	0.604		
DBP (mmHg)	1.010 (0.970–1.051)	0.635		
HOMA-IR	1.775 (1.344–2.345)	<0.001	1.739 (1.322–2.287)	<0.001
TC (mmol/L)	1.343 (0.653–2.763)	0.423		
TG (mmol/L)	0.945 (0.745–1.198)	0.638		
LDL-C (mmol/L)	1.050 (0.482–2.290)	0.901		
HDL-C (mmol/L)	0.551 (0.162–1.881)	0.342		
CRP (mg/L)	1.302 (1.126–1.506)	<0.001	1.243 (1.086–1.423)	0.002
Chemerin (μg/L)	1.038 (1.021–1.054)	<0.001	1.030 (1.016–1.045)	<0.001
Obesity, *n* (%)	1.275 (0.616–2.639)	0.513		
Diatetes, *n* (%)	1.913 (0.507–7.210)	0.338		
CAD, *n* (%)	1.138 (0.283–4.576)	0.855		

BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol; OSAS, obstructive sleep apnea syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

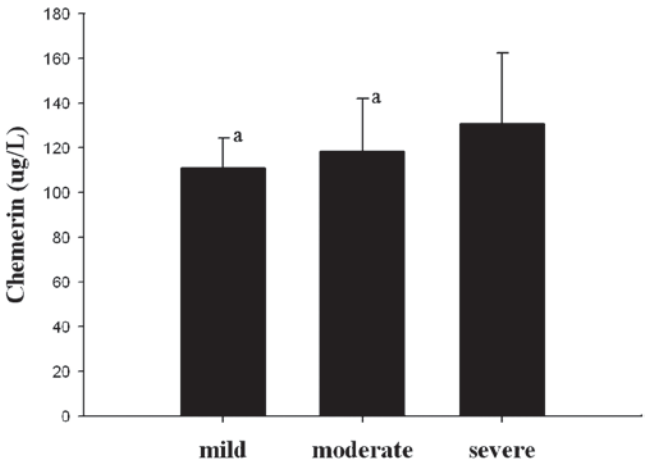

Figure 1. Serum chemerin levels in mild, moderate and severe obstructive sleep apnea syndrome (OSAS) patients. Severe OSAS patients had significantly higher serum chemerin levels (111.01 ± 13.49 μg/L) compared with those in mild (118.33 ± 23.77 μg/L) and moderate (130.99 ± 31.26 μg/L) OSAS patients. However, there were no differences in serum chemerin levels between mild and moderate OSAS patients. [a]Significant vs. serum chemerin levels in severe OSAS patients.

The association of serum chemerin level with other clinical characteristics

Simple linear regression analyses show that serum chemerin levels in OSAS patients were weakly correlated with WC, BMI, SBP, HOMA-IR, CRP, and AHI (Table 3). Then variables including WC, BMI, SBP, HOMA-IR, CRP, and AHI were incorporated into the stepwise linear

regression model (Table 3). Multiple stepwise regression analysis shows that only CRP (β = 0.186, $p = 0.037$) remained weakly associated with serum chemerin. Figure 2 shows the correlation between CRP and serum chemerin levels.

Discussion

Our study indicated that serum chemerin levels were significantly elevated in OSAS patients compared with healthy subjects. Multivariable logistic regression analysis revealed that serum chemerin levels were an independent determinant of the presence of OSAS.

Table 3. Linear regression analyses between chemerin and other clinical parameters.

	Simple regression		Multiple regression	
Parameters	*r*	*p*	Bs	*p*
Age (years)	0.058	0.371		
WC (cm)	0.164	0.008	0.107	0.241
BMI (kg/m^2)	0.158	0.014	0.049	0.594
SBP (mmHg)	0.135	0.037	0.087	0.325
DBP (mmHg)	0.101	0.120		
HOMA-IR	0.140	0.031	0.053	0.562
TC (mmol/L)	0.073	0.262		
TG (mmol/L)	0.062	0.343		
LDL-C (mmol/L)	0.054	0.404		
HDL-C (mmol/L)	0.051	0.417		
CRP (mg/L)	0.202	0.002	0.186	0.037
AHI	0.152	0.022	0.078	0.371
ODI	0.067	0.312		
Average SpO2 (%)	0.075	0.248		
SpO2 < 90% (min)	0.086	0.192		

The overall R^2 for multiple regression is 0.076.
AHI, apnea–hypopnea index; BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; LDL-C, low-density lipoprotein cholesterol; ODI, oxyhaemoglobin desaturation index; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

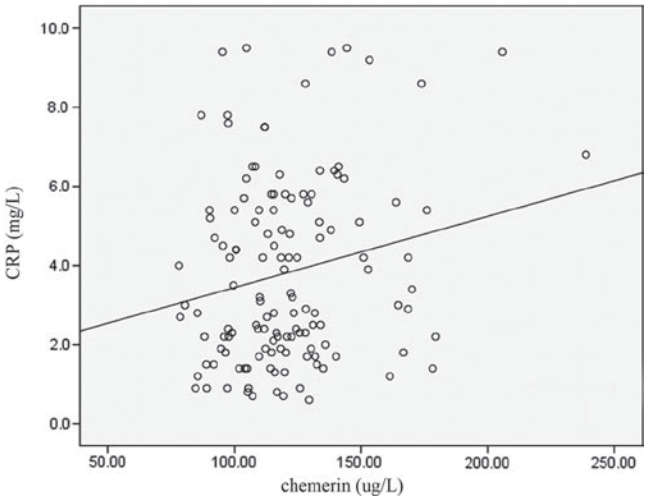

Figure 2. The correlation between C-reactive protein and serum chemerin level.

Serum chemerin levels in severe OSAS patients were significantly higher compared with those in mild and moderate OSAS patients. In addition, serum levels of chemerin were weakly correlated with WC, BMI, SBP, HOMA-IR, CRP, and AHI in patients with OSAS. This is the first study to demonstrate that elevated levels of serum chemerin are associated with the presence and severity of OSAS.

OSAS is now considered to be a major illness that causes great medical morbidity and mortality to millions of people worldwide (Madani et al. 2009). In addition, OSAS is a major predisposing factor for several systemic diseases, such as hypertension, cardiovascular disease, stroke, diabetes, and even sexual dysfunction (Madani et al. 2009). Therefore, it is necessary to assess the risk of OSAS earlier and then to target strategies to prevent or treat OSAS. The current results revealed that serum levels of chemerin were significantly elevated in patients with OSAS compared with healthy controls. This indicates that chemerin may be involved in the pathophysiology of OSAS. Elevated levels of serum chemerin could serve as a new biomarker to predict the presence of OSAS. Recent studies have focused on the important role of adipokines in the mechanism of OSAS. Other adipokines, such as adiponectin, leptin, visfatin, and resistin were also demonstrated to be associated with the development of OSAS (Masserini et al. 2006, Yamamoto et al. 2008, Acıoğlu et al. 2010, Basoglu et al. 2011). These results point to an important role of adipose tissue and adipokine in the pathophysiology of OSAS. Our results also suggested that chemerin levels were correlated with AHI. Serum chemerin levels in severe OSAS patients were significantly higher compared with those in mild and moderate OSAS patients. This indicates that chemerin levels are associated with the severity of OSAS. Hence, serum chemerin levels are suggested to be an independent predicting marker of the presence and severity of OSAS.

Obesity, a chronic disease that has become epidemic all over the world, is considered as a major risk factor for OSAS (Sunitha et al. 2009). The prevalence of OSAS in obese or severely obese subjects is nearly twice as that of normal-weight subjects (Romero-Corral et al. 2010). Patients with mild OSAS who gain 10% of their body weight are at a 6-fold increased risk of developing OSAS, and an equivalent weight loss can result in a more than 20% improvement in OSAS severity (Peppard et al. 2000). In addition, prospective epidemiologic studies have demonstrated that OSAS (especially reduced sleeping time) predisposes to obesity (Hasler et al. 2004). Therefore, obesity may interact with OSAS and then leads to worse outcomes. Our results showed that serum chemerin levels were weakly correlated with WC and BMI. This indicates that chemerin may serve as a link between obesity and OSAS. However, the exact mechanism needs to be explored by further studies.

Recent evidences indicated that chemerin is correlated with inflammation. Significantly elevated levels of the

pro-inflammatory cytokines IL-6, interleukin-8, tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and the matrix metalloproteases were detected after chemerin stimulation in human articular chondrocytes (Berg et al. 2010). Chemerin was also found to contribute to inflammation by promoting macrophage adhesion to vascular cell adhesion molecule 1 (VCAM-1) and fibronectin through clustering of very late antigen-4 (VLA-4) and VLA-5. Another study indicated that chemerin could increase the expression of chemokine (C-C motif) ligand 2 and toll-like receptor 4 (TLR4) in synovial fibroblasts of patients with rheumatoid arthritis and osteoarthritis (Eisinger et al. 2011). Inflammation plays an important role in the development of OSAS (Hart et al. 2010). Therefore, chemerin is hypothesized to be involved in the mechanism of OSAS through inflammatory pathway. The current study indicated that serum chemerin levels were weakly associated with serum CRP. This is consistent with other studies, which also demonstrated a significant association between serum chemrin levels and CRP (Weigert et al. 2010, Yamamoto et al. 2010, Dong et al. 2011, Hu et al. 2011). Furthermore, serum chmerin levels were shown to be associated with other inflammatory markers such as IL-6 and TNF-α (Lehrke et al. 2009). These inflammatory markers have been suggested to be elevated in patients with OSAS (Ye et al. 2007, Yamamoto et al. 2008, Bhushan et al. 2009). This indicates that chemerin may contribute to the presence of OSAS partly through activating different inflammatory pathway and then leads to elevated levels of different inflammatory markers.

The present study has several limitations. First, the sample size is relatively small. Further study in a larger sample is required to determine the differences of serum chemerin levels between OSAS patients and healthy controls. Second, this study was cross-sectional, so our findings should be validated in long-term prospective studies. Third, we did not asses whether continuous positive airway pressure (CPAP) treatment has an effect on the serum levels of chemerin. Then further research is needed to investigate the effect of CPAP on chemerin levels.

In conclusion, this study showed that serum chemerin levels were elevated in OSAS patients compared with healthy controls. Serum chemerin levels in severe OSAS patients were significantly higher compared with those in mild and moderate OSAS patients. Elevated serum chemerin levels are suggested to be an independent predicting marker of the presence and severity of OSAS.

Declaration of interest

The authors report no conflict of interest.

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