

# Significance of vaspin in obstructive sleep apnea-hypopnea syndrome

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**Abstract.** Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a commonly-diagnosed chronic sleep disorder. It is considered to be an important independent risk factor in the development of insulin resistance (IR). Patients with OSAHS exhibit a variety of metabolic disorders, including obesity and metabolic syndrome. Visceral adipose tissue-derived serpin (vaspin) is an adipokine that is considered to be a link between obesity and IR. The present study aimed to evaluate the levels of plasma vaspin in patients with OSAHS and examine their potential correlation with sleep characteristics. A total of 20 healthy male subjects and 42 male patients with OSAHS were selected, and patients were divided into mild (n=22) and severe (n=20) OSAHS groups. The 20 patients in the severe OSAHS group received nasal continuous positive airway pressure (nCPAP) treatment for 2 months. Venous blood samples were drawn from all patients in a fasting state prior to and subsequent to nCPAP treatment, which were used to measure the levels of biochemical indicators. The sleep parameters and serologic index changes were compared prior to and following treatment. The values of contractive pressure (SBP), neck circumference (NC), waist circumference (WC), waist-to-hip ratio (WHR), body mass index (BMI) and hip circumference (HC) in the two OSAHS groups were significantly increased compared with those in the control group. In addition, the levels of vaspin in OSAHS patients were markedly increased and vaspin was revealed to be positively associated with fasting blood sugar, fasting insulin, triglycerides, homeostasis model assessment-IR, apnea-hypopnea index (AHI), NC, WC, BMI and WHR ( $P<0.05$ ). After 2 months of nCPAP treatment, the SBP and AHI were significantly reduced. In conclusion, vaspin may have an important role in OSAHS patients with

IR and treatment using nCPAP may improve the condition of OSAHS patients.

## Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) is a common breathing disorder. It is characterized by repetitive collapse of the upper airway during sleep, resulting in impedance to airflow and hypoxia (1). The symptoms of OSAHS include loud snoring, episodes of breathing cessation, gasping and choking sensations that rouse the patient from sleep, nocturia and insomnia (2). Use of nasal continuous positive airway pressure is the primary treatment in adult OSAHS cases (3). The prevalence of OSAHS increases with age and its prevalence in men is significantly higher than that of women of child-bearing age. However, the prevalence in women increases following menopause (4). OSAHS has been reported to be associated with obesity and metabolic syndrome in adults and is an independent risk factor in the development of insulin resistance (IR) (5). Thus far, the underlying mechanisms linking OSAHS and metabolic syndrome remain poorly understood.

Adipokines are a group of biologically active molecules secreted by the white adipose tissue. Adipokines effect a key role in the regulation of glucose and lipid metabolism, as well as in energy homeostasis (6). Visceral adipose tissue-derived serpin (vaspin) is an adipokine that is a member of the serine protease inhibitor family (7). Evidence has demonstrated that vaspin contributes to the development of IR and type 2 diabetes mellitus (8). In the present study, vaspin was hypothesized to be a possible link between metabolic syndrome and OSAHS.

The aim of the present study was to investigate the possible role of vaspin in the pathogenesis of OSAHS. For this purpose, the serum vaspin level in patients with OSAHS was measured prior to and following medical therapy. In addition, the association between serum vaspin and metabolic variables was analyzed.

## Materials and methods

**Subjects.** The study protocol was approved by the Ethical Committee of the Second Hospital of Shandong University (Jinan, China). All patients provided written informed consent. A total of 42 male patients with OSAHS, aged 34 to 62 years

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old, were enrolled into the study, along with 20 age-matched healthy males that served as the controls. Only male patients were examined in the current study, as gender affects vaspin levels; Körner *et al* (9) reported that vaspin serum levels were significantly higher in girls than in boys. Furthermore, Li *et al* (8) revealed that fasting plasma vaspin levels were significantly higher in female compared with male patients in normal glucose tolerance and impaired glucose tolerance subjects. The incidence of OSAHS is higher significantly in men than women, so male patients were selected. These patients were admitted to the Second Hospital of Shandong University between May 2011 and October 2012, with symptoms such as loud snoring, gasping and choking sensations during sleep and insomnia. The diagnosis of OSAHS was established according to the international diagnostic criteria (10). Apnea was defined as episodes of airflow cessation lasting for >10 sec. Hypopnea was defined as >50% reduction of airflow below the standard level, in addition to a 4% decrease in oxyhemoglobin saturation in patients breathing normally during sleep. The sum of time spent in apnea and hypopnea, determined by an overnight sleep study using polysomnography, was divided by the total sleep time in order to determine the apnea-hypopnea index (AHI). Subjects with an AHI of  $\geq 5$  were considered to suffer from OSAHS. According to the degree of AHI and the arterial oxygen saturation ( $\text{SaO}_2$ ), the subjects were divided into two groups: The mild ( $n=22$ ) and severe ( $n=20$ ) OSAHS groups. In the mild group, the AHI of patients was between 5 and 20, and the lowest  $\text{SaO}_2$  ( $\text{LSaO}_2$ ) values were between 85 and 89%. In the severe group, the AHI value was >21, while the  $\text{LSaO}_2$  was <85%. Subjects with diabetes mellitus, cardiovascular and cerebrovascular diseases, chronic renal failure and chronic respiratory diseases were excluded from the study.

*Clinical and biochemical measurements.* After 12 h of fasting, the subjects underwent anthropometric evaluation. Their height, weight, neck circumference (NC), waist circumference (WC) and hip circumference (HC) were measured by a trained nurse. Body mass index (BMI) was calculated as the body weight in kilograms divided by the square of the height in metres [ $\text{BMI} = \text{weight (kg)} / \text{height}^2 \text{ (m)}$ ]. The waist-to-hip ratio (WHR) was defined as the WC divided by the HC. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were also measured.

After 12 h of fasting, 5-6 ml venous blood was collected from each of the patients, prior and subsequent to treatment. The samples were centrifuged at 1,000-1,200  $\times$  g and kept at  $-80^\circ\text{C}$  until required for subsequent assays. The level of fasting plasma glucose (FPG) was measured by the glucose-oxidase method (11). In addition, fasting insulin (FINS) was assessed using a human insulin-specific radioimmunoassay kit (Linco Research, Inc., St. Louis, MO, USA). Triglyceride (TG) levels, total cholesterol (TC), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein cholesterol were measured using the UniCel Dx C 800 analyzer (Beckman Coulter, Inc., Brea, CA, USA). Furthermore, the vaspin and adiponectin (APN) levels were measured using human Serpin A12/Vaspin quantikine and human total adiponectin/Acrp30 quantikine ELISA kits (R&D Laboratories, Inc., Antrim, UK), respectively, according to the manufacturer's instructions. The intra-assay (describing the variation of results within the data

set) and interassay coefficients of variation (describing the variation of results from repeated experiments) for vaspin and adiponectin were 9% and 11%, respectively. The IR index was then calculated by homeostasis model assessment (HOMA-IR) based on the FPG and insulin concentrations using the equation:  $\text{HOMA-IR} = \text{FPG (mmol/l)} \times \text{FINS (mIU/l)} / 22.5$

*Treatment of severe OSAHS group.* The 20 patients in the severe OSAHS group received nasal continuous positive airway pressure (nCPAP) treatment for 2 months, but the mild OSAHS group received no treatment. nCPAP treatment was selected as the most effective and least invasive treatment method. Prior to the treatment, the patients were informed regarding the details and necessity of the treatment. Subsequently, the patients were treated using an automatic voltage regulator ventilator (ResMed S8 AutoSet II; ResMed, San Diego, CA, USA) at the hospital for 1 night. The patients were treated with continuous ventilation using a nasal mask, which ensured that the patient's respiratory tract remained unobstructed at night in order to correct the apnea and reduce the hypoxic effects. Patients were taught to use the equipment by a trained specialist nurse. Patients then underwent a night of nCPAP treatment, during which a number of parameters were determined with polysomnography. The patients almost all required long-term treatment at home for at least 4 h per night, and these were followed-up for 2 months. An E-series polysomnographer (Compumedics Ltd., Abbotsford, Australia) was used to measure and record the overnight polysomnographic parameters, including an electroencephalogram (in order to distinguish the sleep stage), electrocardiogram (in order to record changes in the heart rate), oronasal airflow (in order to analyze the presence of apnea), chest and abdominal movements by strain gauges, and pulse oxygen saturation. After 2 months of treatment and follow-up, the 20 patients with severe OSAHS were subjected to the same clinical and biochemical measurements as prior to treatment.

*Statistical analysis.* All data are presented as the mean  $\pm$  standard deviation, and were analyzed using SPSS 18.0 software (SPSS, Inc., Chicago, IL, USA). Prior to analysis, the data were assessed for normality of distribution using the Shapiro-Wilk test. The data were analyzed using one-way analysis of variance, Pearson's correlation and stepwise multiple regression analysis. A value of  $P < 0.05$  was considered to indicate a statistically significant difference.

## Results

*Baseline characteristics of the patients.* The baseline characteristics of the controls and OSAHS patients are listed in Table I. Within the total of 62 male patients included in the present study, 42 of these suffered from OSAHS. The mild group included 22 cases, the severe group included 20 cases, and 20 males were enrolled in the control group. No statistically significant differences were observed in age between the three groups ( $P > 0.05$ ). Compared with the control group, the values of SBP, DBP, NC, WC, WHR, BMI and HC in the two OSAHS groups were significantly increased ( $P < 0.05$ ). Compared with the mild OSAHS group, the WC, BMI and HC in the severe OSAHS group were considerably increased,

Table I. Baseline characteristics of controls and patients with OSAHS (mean  $\pm$  standard deviation).

Characteristics	Control group (n=20)	Mild OSAHS group (n=22)	Severe OSAHS group (n=20)
Mean age (years)	46.75 $\pm$ 11.19	47.90 $\pm$ 12.23	49.25 $\pm$ 11.42
SBP (mmHg)	130.25 $\pm$ 8.92	133.58 $\pm$ 11.35 <sup>a</sup>	134.96 $\pm$ 12.45 <sup>a</sup>
DBP (mmHg)	72.28 $\pm$ 6.78	78.61 $\pm$ 10.50 <sup>a</sup>	80.31 $\pm$ 8.15 <sup>a</sup>
NC (cm)	35.73 $\pm$ 1.37	37.70 $\pm$ 2.31 <sup>a</sup>	38.72 $\pm$ 3.62 <sup>a</sup>
WC (cm)	82.31 $\pm$ 6.85	94.19 $\pm$ 7.64 <sup>a</sup>	98.23 $\pm$ 8.49 <sup>a,b</sup>
WHR (cm)	0.84 $\pm$ 0.08	0.93 $\pm$ 0.06 <sup>a</sup>	0.95 $\pm$ 0.08 <sup>a</sup>
BMI	24.28 $\pm$ 1.52	25.91 $\pm$ 2.43 <sup>a</sup>	27.11 $\pm$ 1.87 <sup>a,b</sup>
HC (cm)	97.06 $\pm$ 9.35	101.33 $\pm$ 8.83 <sup>a</sup>	103.12 $\pm$ 9.62 <sup>a,b</sup>
AHI (times/h)	3.30 $\pm$ 1.03	11.00 $\pm$ 2.61 <sup>a</sup>	29.95 $\pm$ 8.15 <sup>a,b</sup>
Average SaO <sub>2</sub> (%)	97.10 $\pm$ 1.55	87.27 $\pm$ 1.42 <sup>a</sup>	78.30 $\pm$ 5.01 <sup>a,b</sup>
FPG (mmol/l)	4.88 $\pm$ 0.28	5.00 $\pm$ 0.46	5.24 $\pm$ 0.32 <sup>a,b</sup>
FINS (mU/l)	13.12 $\pm$ 1.71	15.99 $\pm$ 1.31 <sup>a</sup>	17.91 $\pm$ 2.63 <sup>a,b</sup>
TG (mmol/l)	1.19 $\pm$ 0.27	1.66 $\pm$ 0.29 <sup>a</sup>	1.90 $\pm$ 0.27 <sup>a,b</sup>
TC (mmol/l)	4.57 $\pm$ 0.47	4.70 $\pm$ 0.50	5.09 $\pm$ 0.67 <sup>a,b</sup>
HDL (mmol/l)	1.57 $\pm$ 0.22	1.52 $\pm$ 0.26	1.35 $\pm$ 0.39 <sup>a,b</sup>
LDL (mmol/l)	2.46 $\pm$ 0.51	2.42 $\pm$ 0.43	2.87 $\pm$ 0.62 <sup>a,b</sup>
HOMA-IR	2.84 $\pm$ 0.26	3.56 $\pm$ 0.46 <sup>a</sup>	4.17 $\pm$ 0.48 <sup>a,b</sup>
Vaspin (ng/ml)	1.48 $\pm$ 0.25	1.78 $\pm$ 0.45 <sup>a</sup>	1.85 $\pm$ 0.32 <sup>a</sup>
APN (ng/ml)	10.53 $\pm$ 2.36	8.63 $\pm$ 1.43 <sup>a</sup>	8.77 $\pm$ 1.34 <sup>a</sup>

<sup>a</sup>P<0.05 vs. control group; <sup>b</sup>P<0.05 vs. mild group. OSAHS, obstructive sleep apnea-hypopnea syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; NC, neck circumference; WHR, waist-to-hip ratio; BMI, body mass index; AHI, apnea-hypopnea index; SaO<sub>2</sub>, arterial oxygen saturation; FPG, fasting plasma glucose; FINS, fasting insulin; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; vaspin, visceral adipose tissue-derived serpin; APN, adiponectin; WC, waist circumference; HC, hip circumference.

while no significant difference in SBP, DBP, NC or WHR was observed between the two OSAHS groups. The AHI was significantly increased in the mild and severe groups compared with the control group, and between these OSAHS groups (P<0.05). The average SaO<sub>2</sub> was significantly decreased in the severe group compared with the control and mild groups, and between the control and mild groups (P<0.05). In addition, the FPG level in the severe OSAHS group was significantly higher compared with that of the mild OSAHS and control groups (P<0.05), while the FPG level in the mild OSAHS group was not significantly increased compared with that in the control group (P>0.05). Serum FINS, TG levels and HOMA-IR index were significantly increased compared with the control group in the mild and severe groups, and in the severe group compared with the mild group. TC and LDL levels were increased and HDL levels decreased in the severe OSAHS group compared with the mild and the control groups (P<0.05), but no significant difference was observed in levels of these between the control and mild groups (P>0.05). The level of vaspin in the mild and severe OSAHS groups (1.78 $\pm$ 0.45 vs. 1.85 $\pm$ 0.32 ng/ml, respectively) was significantly higher compared with that in the control group (1.48 $\pm$ 0.25 ng/ml; P<0.01); however, no significant difference was observed between the mild and severe groups (P>0.05). APN levels were significantly higher in the control group compared with the two OSAHS groups (P<0.05).

*Study of serum vaspin levels.* Based on the results of Pearson's correlation analysis, the level of vaspin was positively associated with WC, FPG, FINS, HOMA-IR, TG, NC, BMI, WHR, AHI and NC (P<0.05), and negatively associated with SaO<sub>2</sub> and APN level (Table II). Therefore, vaspin was defined as the dependent variable, and WC, WHR, BMI, FPG, FINS, HOMA-IR, TG, AHI, APN and SaO<sub>2</sub> were defined as the independent variables in order to perform multiple linear regression analysis. Multiple stepwise regression analysis showed that HOMA-IR and SaO<sub>2</sub> were independent risk factors that influenced the vaspin levels (Y=2.875-0.021SaO<sub>2</sub> + 0.588 x HOMA-IR; Table III).

*Comparison of values in severe group prior to and following 2 months of nCPAP treatment.* After 2 months of nCPAP treatment, the SBP, AHI and vaspin were significantly reduced and SaO<sub>2</sub> and APN were increased compared with the values prior to treatment (P<0.05). Other indices were not significantly altered (Table IV).

## Discussion

Sleep apnea syndrome accounts for 70% of sleep disorder cases, with OSAHS being the most common type of this syndrome (12). OSAHS can occur at any age and gender, but is most prevalent in males with an age of >40 years. In addition, obesity is an important factor causing upper airway

Table II. Pearson's correlation analysis between vaspin and other variables.

Characteristics	r	P-value
WC	0.286	0.048
FPG (mmol/l)	0.291	0.022
FINS (mU/l)	0.640	<0.001
HOMA-IR	0.627	<0.001
TG (mmol/l)	0.604	<0.001
BMI	0.462	<0.001
WHR	0.465	<0.001
AHI (times/h)	0.595	<0.001
NC (cm)	0.520	0.001
Average SaO <sub>2</sub> (%)	-0.667	<0.001
APN (ng/ml)	-0.398	0.001

Vaspin, visceral adipose tissue-derived serpin; r, correlation coefficient; WC, waist circumference; FPG, fasting plasma glucose; FINS, fasting insulin; HOMA-IR, homeostasis model assessment-insulin resistance; TG, triglycerides; NC, neck circumference; BMI, body mass index; WHR, waist-to-hip ratio; AHI, apnea-hypopnea index; SaO<sub>2</sub>, arterial oxygen saturation; APN, adiponectin.

Table III. Impact factors of vaspin through multiple stepwise regression analysis.

Model	B-value	SE	t-test	P-value
Constant	2.875	0.876	3.283	0.002
SaO <sub>2</sub>	-0.021	0.007	-3.198	0.002
HOMA-IR	0.588	0.284	2.068	0.043

Vaspin, visceral adipose tissue-derived serpin; SE, standard error; SaO<sub>2</sub>, arterial oxygen saturation; HOMA-IR, homeostasis model assessment-insulin resistance.

blockage (13). In the present study, subjects were enrolled into three groups, including the mild OSAHS, severe OSAHS and control groups. The mean age of the three groups was not significantly different ( $P>0.05$ ). The BMI, NC, WC and WHR in the OSAHS groups were markedly higher compared with the values in the control group. Therefore, OSAHS appears to be closely associated with obesity-related indicators. However, obese patients do not necessarily suffer from OSAHS, while certain patients with OSAHS have a normal BMI (14). In the current study, OSAHS patients were found to have an imbalance in body fat distribution, since the NC, WC and WHR in the OSAHS groups were higher compared with those in control subjects with the same BMI. Increased NC indicated that excess fat was deposited around the upper airway, and increased WHR indicated that superfluous fat was deposited in the viscus. Thus, weight reduction may be useful to relieve and treat OSAHS.

OSAHS has been shown to be an independent risk factor of abnormal glucose and lipid metabolism (15). Meslier *et al* (16) showed that the incidence of type 2 diabetes mellitus and

Table IV. Comparison of severe group prior to and following nCPAP treatment.

Index	Prior to treatment	Following treatment
SBP (mmHg)	134.96±12.45	129.27±10.18 <sup>a</sup>
DBP (mmHg)	80.31±8.15	80.25±6.20
AHI	29.95±8.15	18.20±6.45 <sup>a</sup>
Average SaO <sub>2</sub>	78.30±5.01	85.68±6.02 <sup>a</sup>
FPG (mmol/l)	5.24±0.32	5.20±0.39
FINS (mU/l)	17.91±2.63	16.52±2.07
TG (mmol/l)	1.90±0.27	1.81±0.36
TC (mmol/l)	5.09±0.67	5.10±0.82
HDL (mmol/l)	1.35±0.39	1.36±0.53
LDL (mmol/l)	2.87±0.62	2.67±0.49
HOMA-IR	4.17±0.48	4.09±0.57
Vaspin (ng/ml)	1.85±0.32	1.61±0.27 <sup>a</sup>
APN (ng/ml)	8.77±1.34	10.15±1.8 <sup>a</sup>

<sup>a</sup> $P<0.05$  vs. value prior to the nCPAP treatment. nCPAP, nasal continuous positive airway pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; AHI, apnea-hypopnea index; SaO<sub>2</sub>, arterial oxygen saturation; FPG, fasting plasma glucose; FINS, fasting insulin; TG, triglycerides; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment-insulin resistance; vaspin, visceral adipose tissue-derived serpin; APN, adiponectin.

impaired glucose tolerance in OSAHS males was 30.1 and 20.0%, respectively. In the present study, all subjects had a normal FPG level (3.9-6.0 mmol/l). However, the FPG level in the severe OSAHS group was higher compared with that of the control group ( $P<0.05$ ) and non-significantly higher than that in the mild group ( $P>0.05$ ). This might be due to the small sample size used in the present study. The levels of FPG, FINS, HOMA-IR, TG and TC in the OSAHS groups were higher than those in the control group. The HOMA-IR index in the OSAHS groups was positively correlated with BMI and AHI, and negatively correlated with SaO<sub>2</sub>. Therefore, the OSAHS treatment selected should be able to regulate glucose metabolism and prevent the development of diabetes.

As mentioned earlier, OSAHS was shown to be closely associated with obesity-related indicators. Adipose tissue function may play an important role in the pathogenesis of OSAHS. In addition to neutral fat storage, energy storage, energy supply and temperature regulation, adipose tissue is also an endocrine organ with the function of endocrine, autocrine and paracrine signaling (17). Adipose tissue is able to secrete >100 types of adipokines, including leptin, APN, tumor necrosis factor- $\alpha$ , interleukin-6 and vaspin. Adipose tissue also plays an important role in IR and body metabolism (18). Hida *et al* (15) originally identified the new adipokine, vaspin, in visceral adipose tissue of Otsuka Long-Evans Tokushima Fatty rats, and vaspin was found to be part of the serpin superfamily (19). In the present study, the level of serum vaspin was measured and a significant difference was identified between the control and OSAHS groups. The level of vaspin was also found to be

associated with BMI, WL, WHR, TG, HOMA-IR and FINS. Therefore, we speculate that vaspin may be associated with the glucose metabolism, IR and obesity indices. In addition, the level of serum vaspin was positively associated with AHI ( $P<0.05$ ) and negatively associated with  $\text{SaO}_2$  ( $P<0.05$ ); thus, we hypothesize that vaspin is associated with the severity of OSAHS and degree of nocturnal hypoxia. Vaspin was then defined as a dependent variable and multiple linear regression analyses were performed. As shown in the results,  $\text{SaO}_2$  and HOMA-IR were independent of vaspin. Therefore, vaspin is considered to be positively correlated with IR and OSAHS.

A principal and potential damage of OSAHS is the disturbance of the normal sleep structure (20). Microarousal is a neurological event, during which sleep fragmentation is activated, including the autonomic nervous system and multiple neural networks (21). Intermittent hypoxia and sleep fragmentation can activate the sympathetic-adrenal axis (22). In the short-term, this activation can inhibit insulin excretion and stimulate hepatic glucose output. Furthermore, insulin sensitivity in peripheral tissues may be reduced, resulting in IR (23). If left untreated, OSAHS may lead to cardiovascular and cerebrovascular diseases, as well as a variety of complications (22).

nCPAP is an efficient strategy and the main method used to treat OSAHS, with efficiency rates that can reach 70-80%. As shown in numerous studies, subsequent to nCPAP, the time of apnea was reduced, hypoxia was corrected, IR was improved and metabolic disorders were recovered (24,25). Furthermore, the treatment can improve the blood metabolism, coronary atherosclerotic heart disease and high blood pressure.

In conclusion, in the present study, the levels of blood pressure, TGs and FINS were decreased following nCPAP treatment in the severe OSAHS group, although the changes were not statistically significant. The non-significant result may be due to the short time of nCPAP treatment. Nevertheless, a beneficial effect of nCPAP treatment in OSAHS patients was observed.

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