Journal of
Cardiology and Vascular Medicine

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Research Article Open Access

Effect of Nasal Continuous Positive Airway Pressure on Plasma Asprosin, Chemerin and ANGPTL4 Levels in Patients with Obstructive Sleep Apnea

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Received Date: March 12, 2021 **Accepted Date:** April 12, 2021 **Published Date:** April 14, 2021

Citation: Wang Hao-hua (2021) Effect of Nasal Continuous Positive Airway Pressure on Plasma Asprosin, Chemerin and ANGPTL4 Levels in Patients with Obstructive Sleep Apnea. J Cardio Vasc Med 7: 1-8.

Abstract

Aim: Obstructive sleep apnea (OSA) is associated with insulin resistance and cardiovascular disease. Adipokine has been suggested to play a role in the development of these diseases through their role in regulating the metabolism of plasma lipid molecules. This study was designed to evaluate the effect of nasal continuous positive airway pressure (CPAP) on plasma asprosin, chemerin and angiopoietin-like 4(ANGPTL4) levels in patients with OSA.

Method: Fifty subjects with newly diagnosed OSA and fifty healthy individuals were enrolled. Patients were admitted with nasal CPAP treatment for 6 months. Plasma asprosin, chemerin and ANGPTL4 levels, as well as brachial–ankle pulse wave velocity (ba-PWV) and ankle–brachial index (ABI), were measured at baseline and after treatment.

Results: Plasma chemerin levels, BMI, HOMA-IR and ba-PWV were significantly higher ($P< 0.05$, respectively), whereas plasma asprosin, ANGPTL4 levels and ABI were significantly lower in patients with OSA than those in healthy individuals ($P< 0.05$, respectively). After treatment, the patients showed higher plasma asprosin ANGPTL4 levels, and ABI ($p<0.05$), while plasma chemerin levels, BMI, HOMA-IR and ba-PWV were lower ($p<0.05$). The changes in HOMA-IR, ba-PWV and ABI were correlated with the changes in plasma asprosin, chemerin and ANGPTL4 levels over the study period ($p<0.05$).

Conclusion: Nasal CPAP treatment exhibited significant changes in plasma asprosin, chemerin and ANGPTL4 levels, which may contribute to improve insulin resistance and endothelial function in patients with OSA.

Keywords: Obstructive sleep apnea; endothelial function; insulin resistance; Adipokine; CPAP

Introduction

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder and becoming increasingly prevalent worldwide. It is characterized by repetitive collapse of the upper airway during sleep, resulting in imped¬ance to airflow and hypoxia l [1]. OSA has been recognized as a major health problem associated with the increased risk of insulin resistance and cardiovascular diseases [2–3].

The adipose tissue of the human body is not only an organ that stores energy but also an endocrine tissue that is active in metabolism. It secretes hormones and a variety of other biologically active substances and participates in maintaining many physiological functions of the body. The adipokines chemerin and angiopoietin-like 4 (ANGPTL4) are involved in the occurrence and progression of insulin resistance in patients with OSA [4-5]. Asprosin is a novel regulatory adipokine that was discovered in recent years to be involved in the pathogenesis of insulin resistance [6]. However, there is few studies on the relationship among asprosin, chemerin, ANGPTL4 and insulin resistance in patients with OSA.

Epidemiological studies have shown significant independent associations between OSA and hypertension, coronary artery disease, arrhythmias, heart failure, and stroke [3]. Endothelial dysfunction is the early development of atherosclerosis and consequently cardiovascular complications [7]. Brachial–ankle pulse wave velocity (ba-PWV) and ankle–brachial index (ABI) are widely used indicators of arterial elasticity and stiffness, reflecting endothelial dysfunction [8]. Ba-PWV and ABI abnormalities appear at early stages of OSA [9]. Recent studies have shown that adipokine acts as an important regulatory molecule in cardiovascular diseases [10]. In the present study, asprosin, chemerin, ANGPTL4 were hypothesized to be a possible link between endothelial function and OSA.

Nasal continuous positive airway pressure (CPAP) is the most effective treatment used to improve nocturnal desaturation in patients with OSA [9]. Nasal CPAP therapy has been shown to improve insulin resistance and endothelial function in patients with OSA [10], but the mechanisms are not fully understood. In the present study, we focused on the effect of nasal CPAP therapy on plasma asprosin, chemerin and ANGPTL4 levels, due to their important roles in the pathogenesis of insulin resistance and atherosclerosis in patients with OSA (Table 1).

Table 1: Clinical and biochemical characteristics in OSA patients as well as in control groups $\overline{x} \pm s$

	controls	**Patients with OSA**	
		Before treatment	After treatment
Number of subjects	50	50	50
Age (years)	35.1±1.2	36.5±2.1	36.8±2.2
BMI (kg/m2)	24.1±2.3	27.5±2.1**	24.8±2.2♀
FPG (mmol/L)	4.75±1.12	5.09±1.23	4.93±1.22
TC (mmol/L)	4.54±1.55	4.82±1.12	4.59±1.33
LDL-C (mmol/L)	2.33±1.11	2.89±1.32	2.23±1.26
HDL-C (mmol/L)	1.58±0.35	1.17±0.57	1.32±0.61
TG(mmol/L)	1.15±0.88	1.77±0.82*	1.37±0.95♀
HOMA-IR	2.33±1.33	4.45±1.26*	2.55±1.47 ♀♀
asprosin (ng/mL)	15.57±3.11	6.64±1.79*	11.69±2.32♀
chemerin (ng/mL)	73.2±21.2	106.70±10.17*	84.01±12.22♀
ANGPTL4 (pg/mL)	36.88±5.11	19.78±5.49	29.98±6.03♀
Ba-PWV(cm/s)	1211±218	1585±212*	1388±205♀
ABI	1.15±0.34	0.85±0.23*	0.98±0.13♀
AHI	3.4±1.5	28.5±5.5**	11.3±3.3♀♀

* $p < 0.05$, * * $p < 0.001$, compared with control, ♀$p < 0.05$, compared with patients before treatment; ABI ankle–brachial index, AHI apnea–hypopnea index,ANGPTL4 angiopoietin-like 4, Ba-PWV brachial–ankle pulse wave velocity, FPG fasting glucose, HOMA-IR homeostasis model assessment of insulin resistance, HDL-C high-density lipoprotein cholesterol, LDL-C low-density lipoprotein cholesterol, TC total cholesterol,TG triglyceride

Material and Methods

Subjects

From June 2018 to June 2020, fifty newly diagnosed patients with OSA were studied, fifty healthy subjects served as control. Exclusion criteria were similar to that in the previous study [11]. The exclusion criteria are as follows: chronic liver disease or chronic renal failure; diabetes mellitus; thyroid dysfunction; malignancies; use of corticosteroids or antibiotics over the 4w preceding recruitment in the study; heart failure, lung disease, cerebrovascular disease, kidney disease.

Patients were administered with nasal CPAP therapy for 6 months. This study has been reviewed by an appropriate ethics committee and has been conducted in accordance with the ethical standards laid down by the 1964 Declaration of Helsinki. Written informed consent was obtained from all subjects.

Laboratory methods

The procedure was described previously [12]. Venous blood samples were drawn after a 12- to 14-h overnight fast. Plasma samples were analyzed for asprosin, ANGPTL4 and chemerin content by ELISA (Shino-Test, IBL) according to the manufacturer's instructions, with samples diluted 1 to 2 in assay buffer and a standard curve ranging from 80ng/mL to 300 pg/mL. Plasma samples were diluted 1 to 3 and measured in duplicate, and the results were averaged.

The intra-assay coefficient of variation was 5- 6.5%. The levels of triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HbA1c and other conventional biochemical parameters were measured on an automatic analyzer. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) defined as fasting glucose (mmol/L)* fasting insulin (mu/L)/22.5.

The apnea–hypopnea index (AHI) is evaluated by the recommendations of the American Academy of Sleep Medicine [13].

The Omron automatic arteriosclerosis detector (BP-203RPEIII) was used, the room temperature was maintained at approximately 25 °C, a pressure-sensitive probe was placed at the location with the most obvious pulsation of the brachial and ankle arteries, the electrodes were connected, the arterial pulse wave waveform was traced for 5 min, and the instrument automatically analyzed and outputted the results. The high value in bilateral limb measurements of ba-PWV and the low value in bilateral measurements of ABI were taken for analysis. The diagnostic criteria were as follows: When ba-PWV was <1400 cm/s, it was defined as normal elasticity of peripheral arteries; when ba-PWV was >1400 cm/s, peripheral arteriosclerosis was considered present. The American College of Cardiology list ABI ≤ 0.90 as the standard cut-off value for the diagnosis of peripheral arterial disease, that is, the possibility of lower extremity.

Clinical Events and Mortality

Comprehensive statistical analysis was conducted with SPSS 20.0 software. The measurement data that were normally distributed are expressed as mean ± SD. Comparisons before vs. after treatment were performed with the paired t test. One-way analysis of variance was used for comparison between groups. Linear regression analyses were used to assess the relation between the nasal CPAP therapy–induced changes in HOMA-IR, ba-PWV, ABI and other variables. $P \leq 0.05$ was considered to be statistically significantly.

Results

All patient characteristics and the results were listed in Table 1.The levels of AHI, BMI, HOMA-IR,TG, chemerin and ba-PWV were higher in patients than those of the healthy individuals($p<0.05$).However, the levels of ANGPTL4, asprosin, and ABI were significant lower in patients as compared to healthy individuals ($p<0.05$). There were no significant differ¬ence in other parameters between patients and healthy individuals.

Treatment with nasal CPAP significantly increased the levels of ANGPTL4, asprosin and ABI and decreased the levels of AHI, BMI, HOMA-IR, TG, chemerin and ba-PWV ($p < 0.05$) (Figures 1, 2 and 3).

Linear correlation coefficients were used to analyze the relationship between changes in HOMA-IR, ba-PWV, ABI and changes in other indices in patients after treatment. The results showed that changes in HOMA-IR, ba-PWV, and ABI were all correlated with changes in asprosin, chemerin and ANGPTL4 ($p<0.05$).

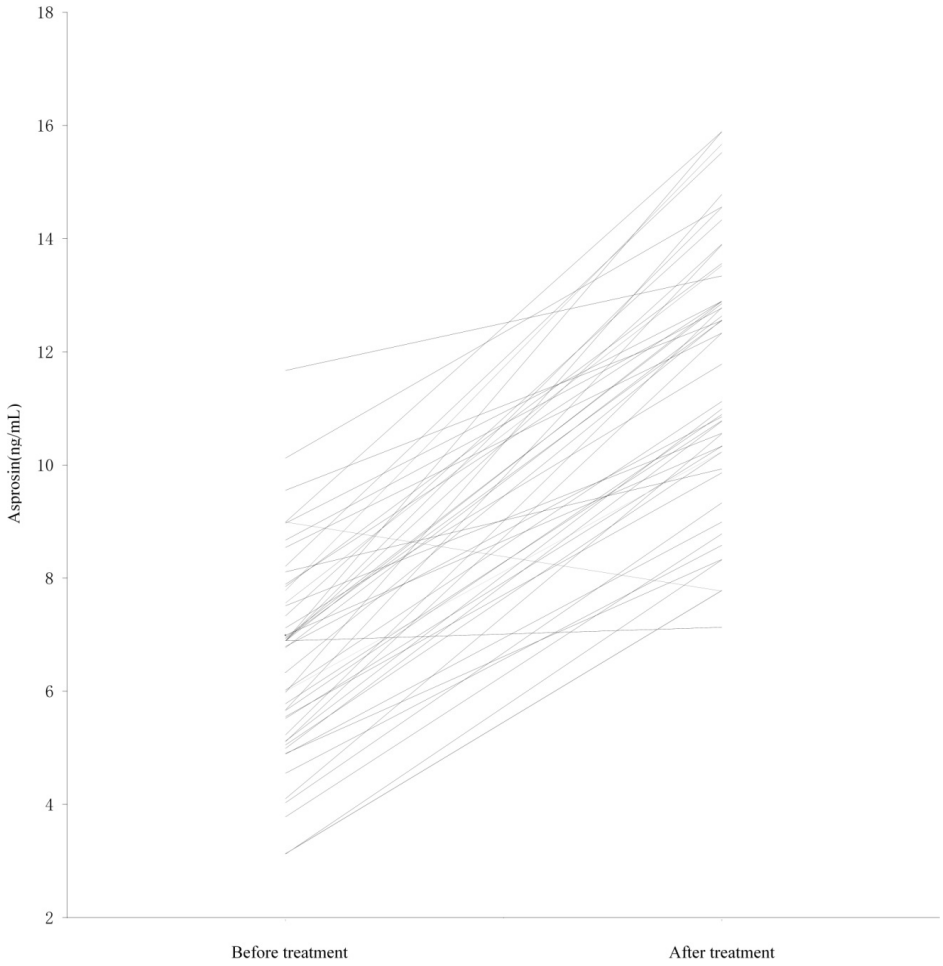

Figure 1: Serum asprosin levels in patients with OSA before and after nasal CPAP treatment

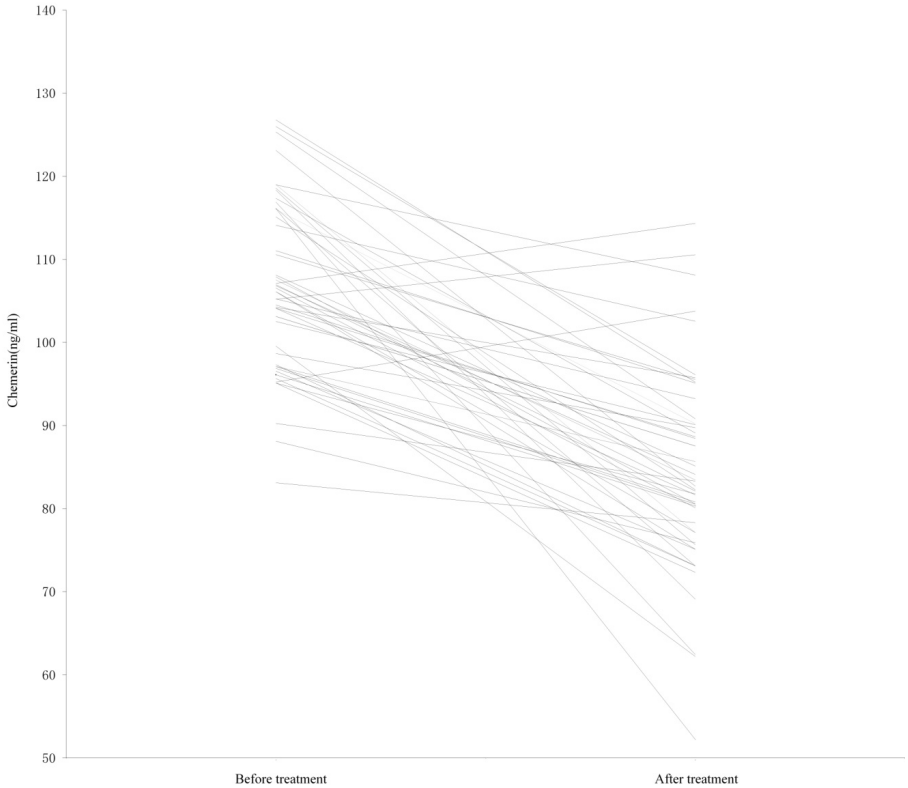

Figure 2: Serum chemerin levels in patients with OSA before and after nasal CPAP treatment

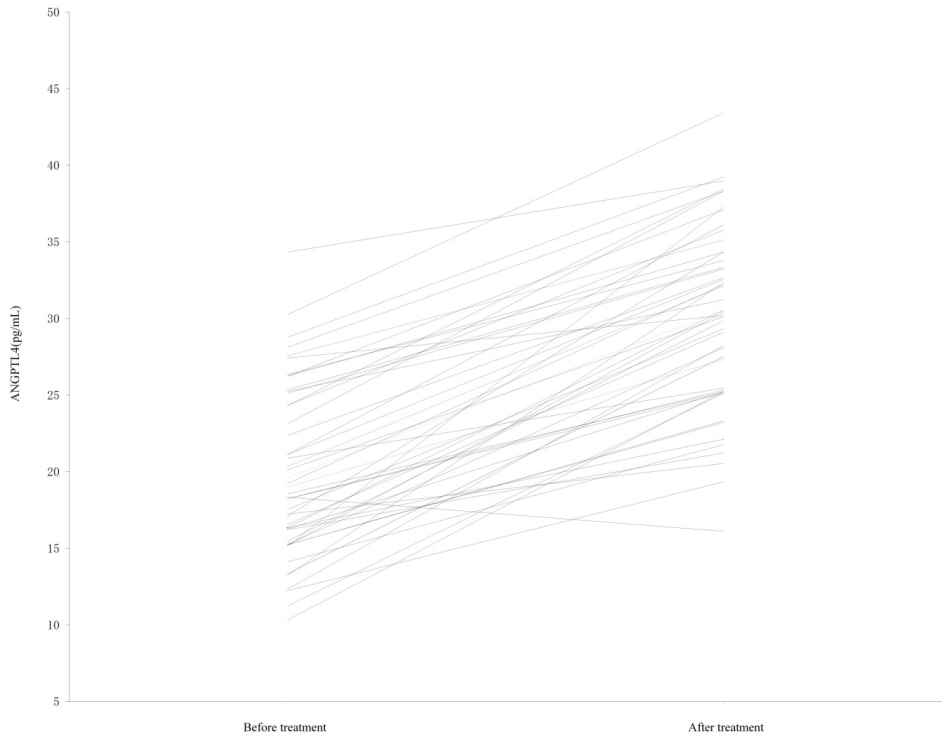

Figure 3: Serum ANGPTL4 levels in patients with OSA before and after nasal CPAP treatment

Discussion

Nasal CPAP treatment represents the most suitable treatment of OSA. In addition, nCPAP improves insulin resistance, and prevents cardiovascular disease in patients with OSA, but the mechanism is not fully understood. Adipokine regulate insulin secretion and insulin sensitivity, and play an important role in the pathogenesis of cardiovascular diseases [4-6]. There are few studies on the effects of nasal CPAP on the plasma levels of asprosin, chemerin and ANGPTL4 in patients with OSA, nor on the relationship among the adipokine above, insulin resistance and endothelial function. Our study for the first time confirmed that nasal CPAP treatment increased plasma ANGPTL4 and asprosin levels in patients with OSA, while plasma chemerin levels were decreased, and that changes in asprosin, chemerin and ANGPTL4 were associated with insulin resistance and endothelial function.

Insulin resistance contributes to the pathogenesis of type 2 diabetes and is closely linked with cardiovascular risk factors. Recent studies have shown that insulin resistance is significantly increased in patients with OSA [2].Plasma asprosin, ANGPTL4 and chemerin play important roles in the occurrence of insulin resistance [4-6]. Our results firstly showed that HOMA-IR in patients with OSA was associated with plasma asprosin, ANGPTL4 and chemerin levels. It is well established that nasal CPAP treatment improved glucose metabolic disturbance and insulin resistance in patients with OSA [14]. Our study supports the observations of rong huang et al. [14] showing that the reduction of BMI, HOMA-IR and TG exited after nasal CPAP treatment. The crucial mechanism of the relationship between nasal CPAP and insulin resistance remain unclear. In the present study, we considered that asprosin, ANGPTL4 and chemerin are involved in the improvement of insulin resistance during the course of nasal CPAP treatment. We measured plasma adipokine levels above in patients with OSA and found that nasal CPAP treatment change the levels of plasma ANGPTL4, chemerin and asprosin. Correlation analysis showed that the change in HOMA-IR in patients over the study period was correlated with the changes in asprosin, ANGPTL4 and chemerin.

It is well established that oxidative stress plays a major role in insulin resistance [15].Additionally; much evidence supports a pivotal role for ANGPTL4, chemerin and asprosin in oxidative stress [16-18]. Stimulation of cardiac ANGPTL4 gene expression protected the heart against fatty acid-induced oxidative stress [16]. Yao J et. have shown the up regulation of chemerin/chemokine-like receptor 1 might contribute to oxidative stress

and apoptosis in the ovaries of obese mice [17]. Asprosin protects mesenchymal stromal cells from oxidative stress-induced apoptosis [18]. There have been few reports on nasal CPAP treatment and oxidative stress. Mora Murri et al have shown that markers of protection against oxidative stress were increased after CPAP in patients with sleep apnea-hypopnea syndrome [19].Besides; CPAP therapy attenuates oxidative stress and nitrate deficiency [20].We hypothesized that nasal CPAP therapy would inhibit the up regulation of chemerin/chemokine-like receptor 1, reduce the secretion of oxidative stress, and induce the expression of asprosin and ANGPTL4, improving insulin resistance and regulating blood lipid metabolism and inflammatory response. In addition, whether asprosin, ANGPTL4 and chemerin can affect each other, whether these cytokines can act as independent factors affecting insulin resistance, and whether there are complex regulatory networks between various cytokines with different functions, thus indirectly affecting insulin resistance, still need to be confirmed by further research.

Nasal CPAP improves endothelial function and delays the onset and progression of atherosclerosis in patients with type OSA [10]. Our research shows that nasal CPAP improves ba-PWV and ABI in patients with OSA, which is consistent with the previous studies. Our correlation analysis showed that the changes in ba-PWV and ABI were correlated with changes in ANGPTL4, chemerin and asprosin.The ANGPTL4, chemerin and asprosin are involved in hyperglycemia, hypertension, obesity, abnormal lipid metabolism, and oxidative stress. These risk factors are all involved in the pathogenesis of atherosclerosis. In the present study, we found that nasal CPAP decreased plasma chemerin levels and increased the levels of ANGPTL4 and asprosin in patients with OSA, thereby controlling blood sugar, blood pressure, obesity, lipid metabolism, and oxidative stress, inhibiting inflammatory responses and protecting the vascular endothelium. Additionally, nitric oxide (NO) is the main signal molecule that regulates vasodilation. Changes in the level of NO in blood vessels can quickly alter vascular tension and thus regulate vascular endothelial function. Chemerin and asprosin are involved in NO production [21-22].We speculate that Nasal CPAP may affect the levels of ANGPTL4, chemerin and asprosin in patients with OSA, thereby promoting NO synthesis, then relaxing the aorta and the resistance of blood vessels and protecting the blood vessel endothelium. In short, nasal CPAP improves endothelial function in patients with OSA and may exert its functions through different mechanisms of action.

The present study has several limitations. Firstly, the enrollment population was limited, the number of samples was small, and the observation time was short. In later studies, the study population and sample size should be further expanded, and the long-term efficacy of nasal CPAP should be evaluated. Secondly, we speculate that nasal CPAP improve the plasma ANGPTL4, chemerin and asprosin levels by inhibiting oxidative stress in patients with OSA. However, there is no comparative study on the effects of oxidative stress inhibitor and nasal CPAP on plasma ANGPTL4, chemerin and asprosin in patients with OSA. Further studies were needed to investigate the effect of nasal CPAP on plasma ANGPTL4, chemerin and asprosin levels in patients with OSA.

Acknowledgments

The authors would like to thank Dr. Xiang Guang-da for excellent technical support and critically reviewing the manuscript.

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