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Original Article

Influence of CPAP therapy on the levels of advanced glycation end products and oxidated low density lipoprotein in patients with OSAHS

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Abstract: To observe and analyze the effects of continuous positive airway pressure (CPAP) ventilation on advanced glycation end products (AGEs) and oxidized low density lipoprotein (ox-LDL) levels in patients with obstructive sleep apnea hypopnea syndrome (OSAHS), 60 patients with OSAHS were selected as the case group, and 30 patients with simple snoring were selected as the control group. The patients were treated with CPAP for 4 weeks. The serum levels of AGEs and ox-LDL of patients in the control group and of OSAHS patients before and after CPAP treatment were compared. Other clinical indexes were observed and compared including age, body mass index (BMI), waist circumference, neck circumference, insulin level, homeostasis model assessment (HOMA) index, systolic blood pressure (SBP), diastolic blood pressure (DBP), apnea hypopnea index (AHI), and lowest observed oxygen saturation (LSaO2). The serum levels of AGEs and ox-LDL in the case group prior to treatment were significantly higher than those in the control group ($t = 6.494, 30.128, P < .05$). After CPAP treatment, the serum levels of AGEs and ox-LDL measured in OSAHS patients decreased significantly ($t = 18.057, 58.556, P < .05$) but were still higher than those in the control group ($t = 2.176, 14.156, P < .05$). After CPAP treatment, patients in the case group showed significant improvement in insulin ($t = 5.198, P < 0.05$), HOMA index ($t = 6.631, P < 0.05$), SBP ($t=5.921, P < 0.05$), DBP ($t = 5.022, P < 0.05$), AHI ($t = 8.025, P < 0.05$) and LSaO2 ($t = -12.016, P < 0.05$). The AHI level after CPAP treatment of the patients with OSAHS was positively correlated with the patients' BMI (standardized regression coefficient = 0.457), neck circumference (standardized regression coefficient = 0.337), HOMA index after the treatment (standardized regression coefficient = 0.669), SBP level after the treatment (standardized regression coefficient = 0.492), the serum AGE level after the treatment (standardized regression coefficient = 0.651), and the serum ox-LDL level after the treatment (standardized regression coefficient = 0.613; $P < .05$). LSaO2 was negatively correlated with the patients' BMI (standardized regression coefficient = -0.415), HOMA index after the treatment (standardized regression coefficient = -0.537), SBP level after the treatment (standardized regression coefficient = -0.336), the serum AGE level after the treatment (standardized regression coefficient = -0.528), and the serum ox-LDL level after the treatment (standardized regression coefficient = -0.611; $P < .05$). In sum, patients with OSAHS show higher serum levels of AGEs and ox-LDL, and the application of CPAP treatment can improve clinical symptoms and reduce the serum AGE and ox-LDL levels of the patients with OSAHS. This reduction may play a role in reducing oxidative stress and regulating metabolism, thereby reducing the risk of cardiovascular and cerebrovascular disease.

Keywords: Continuous positive airway pressure ventilation, obstructive sleep apnea hypopnea syndrome, advanced glycation end products, oxidized low density lipoprotein, curative effect observation

Introduction

Obstructive sleep apnea hypopnea syndrome (OSAHS) refers to a syndrome of repeated, intermittent upper airway blockage during sleep with primary characteristics that include snoring, apnea, superficial and slow respiration, discontinuation of sleep, hypoxemia, and diurnal lethargy [1]. Because of its relatively high prevalence and the potential for damage to multiple target organs, OSAHS poses a serious threat to physical and mental health. OSAHS reduces the patient's quality of life, and its complications can endanger the patient's life and safety. Many recent studies indicate that OSAHS can induce systemic inflammatory reactions and lead to endothelial cell functional abnormalities. OSAHS is an independent risk

Table 1. Comparison between groups: levels of AGEs and ox-LDL in the serum

Groups	Time	AGEs (fluorescent value)	ox-LDL (μg/L)
Case group	Before treatment	5.52±2.03[b,c]	301.64±33.01[b,c]
	After treatment	3.55±1.68[a,c]	213.01±29.07[a,c]
Control group		2.74±1.67[a,b]	145.40±16.18[a,b]

Note: [a]: $P < 0.05$, when compared with before treatment in the case group; [b]: $P < 0.05$ when compared with after treatment in the case group; [c]: $P < 0.05$, when compared with the control group.

factor for the onset of atherosclerosis, cardiovascular disease, and cerebrovascular disease [2]. The development of cardiac and cerebral stroke can promote the occurrence and development of OSAHS. Because strokes and OSAHS are mutually influencing and promoting, a vicious cycle is formed [3]. Continuous positive airway pressure (CPAP) treatment is the common therapeutic method for OSAHS, and it can significantly relieve the hypoxemia induced by OSAHS. Whether CPAP treatment can lower the risk of cardiovascular and cerebrovascular diseases that occur in OSAHS patients has not yet been established. This study observes and analyzes the influence of CPAP treatment on advanced glycation end products (AGE) and oxidated low density lipoprotein (ox-LDL) in patients with OSAHS.

Materials and methods

Participants

OSAHS patients admitted into our hospital from Jan. 2014 to Dec. 2014 were candidates for the case group. Included patients conformed to OSAHS Diagnosis Criteria in Guidelines for Diagnosis and Treatment of Obstructive Sleep Apnea Hypopnea Syndrome (2011 modified edition) formulated by the Sleep Breathing Disorder Study Group of the China Society of Respiratory Disease Study of the Chinese Medical Association. All patients demonstrated repeated onset of apnea and hypopnea 30 times during 7 hours of sleep or an apnea hypopnea index (AHI) ≥ 5 times per hour. Among the case group, 40 were men and 20 were women with a mean age of (48.2±10.6) years. 30 patients with simple snoring during the same period (AHI < 5 times per hour) were included in the control group: 18 men and 12 women with a mean age of (47.6±11.1) years. Exclusion criteria for both the case and control groups were a history of cardiovascular disease, chronic respiratory system disease, thyropathy, or diabetes. The difference between the two groups in terms of age and gender was not statistically significant ($P > 0.05$).

Treatment methods

The patients in the case group were given CPAP treatment. According to the patients' facial features, the soft and durable silica gel membrane nasal masks or nasal-facial masks were adopted and German Trend series automatic voltage regulating CPAP breathing machines were used for treatment. The treatment method was based on Expert Consensus of Clinical Application of Continuous Positive Airway Pressure (CPAP) to OSAHS Patients (draft) formulated by the Sleep Breathing Disorder Study Group of the China Society of Respiratory Disease Study of the Chinese Medical Association. The CPAP treatment duration per night was not less than 6 hours, and the treatment lasted for 4 weeks.

Observation indicators

Fasting peripheral venous blood samples were collected from the subjects in the control group, and from the case group before and after CPAP treatment. Samples were placed into test tubes without anticoagulant and maintained at low temperature. The serum was centrifuged at 4°C at 4200 r/min for 6 minutes within one hour after sampling, and then stored at -70°C for future testing. A fluorescence spectrophotometer was used to determine the level of AGEs in the serum specimens, and the ELISA method was used to determine the level of ox-LDL in serum specimens. Clinical indexes such as age, body mass index, waistline, neck circumference, insulin level before and after treatment, homeostasis model assessment (HOMA) indexes, systolic blood pressure (SBP), diastolic blood pressure (DBP), AHI, and lowest saturation of blood oxygen (LSaO2) were observed and recorded.

Statistical methods

The SPSS 19.0 statistical package was used to establish the database and perform statistical analysis. The results were expressed in the form of (mean ± standard deviation). The independent sample t test was used for inter-group

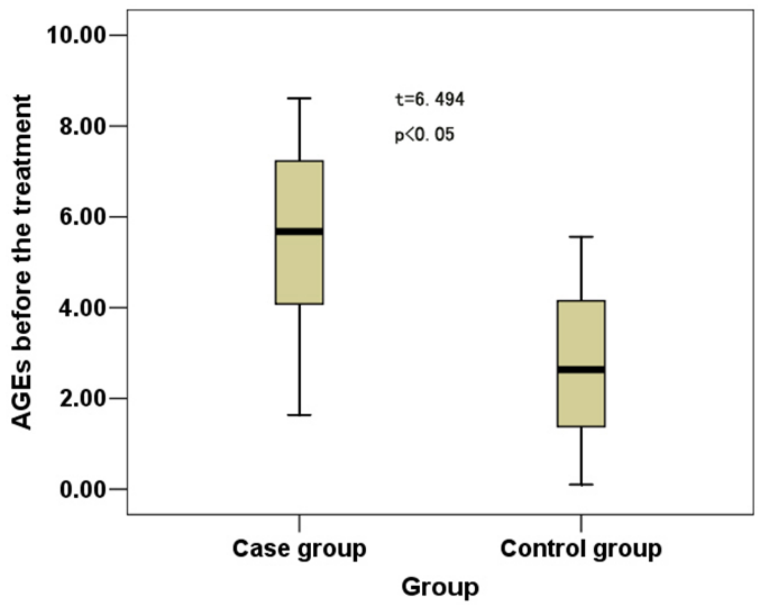

Figure 1. Distribution of serum AGE level before treatment of the subjects in two groups.

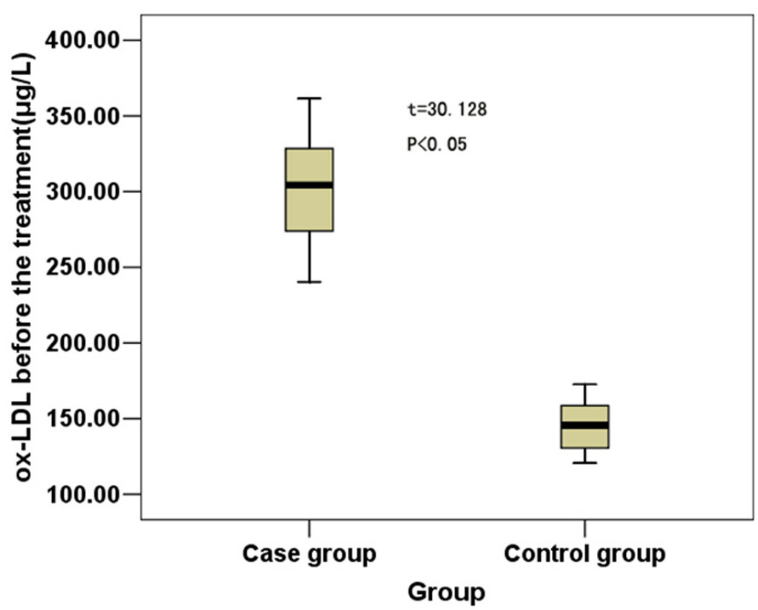

Figure 2. Distribution of serum ox-LDL level before treatment of the subjects in two groups.

comparisons; the paired t-test was used to make comparisons before and after the treatment. Multiple linear regressions were applied to analyze the factors that influenced the patient's post-treatment conditions. The enumeration data were expressed in the form of percentage, and P < 05 meant that the difference was of statistical significance.

Results

Comparison of the levels of AGEs and ox-LDL in the serum

Before CPAP treatment, the levels of AGEs and ox-LDL in the serum of the patients in the case group were significantly higher than those of the control group (t = 6.494, 30.128, P < .05). After the CPAP treatment, the levels of AGEs and ox-LDL in the serum of the patients in the case group dropped significantly (t = 18.057, 58.556, P < .05), but the levels were still significantly higher than those of the control group (t = 2.176, 14.156, P < .05; see **Table 1**). The distribution of the levels of AGEs and ox-LDL in the serum of the subjects in the two groups before and after treatment is shown in **Figures 1-4**.

Comparison of clinical indexes of OSAHS patients before and after CPAP treatment

After CPAP treatment, the clinical indexes of the patients in the case group were significantly improved; see **Table 2**.

Relationship between the condition of OSAHS patients after CPAP treatment and the levels of AGEs and ox-LDL in the serum

A multiple linear regression was performed with AHI and LSaO2 after CPAP treatment as the dependent variables and the patient's clinical indexes such as age, body mass index, waistline, neck circumference, insulin level before and after treatment, HOMA index, SBP, DBP, AGEs level in serum, and ox-LDL level in

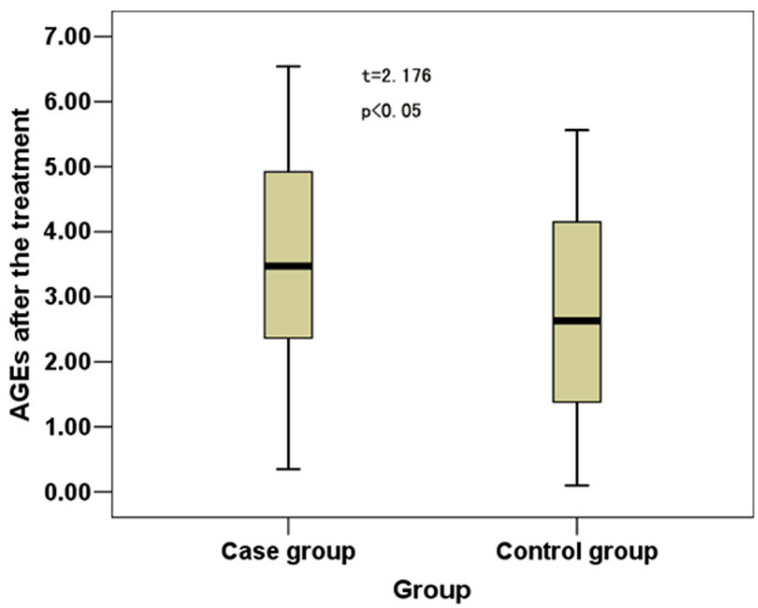

Figure 3. Distribution of serum AGE level after treatment of patients in the case group and the subjects in the control group.

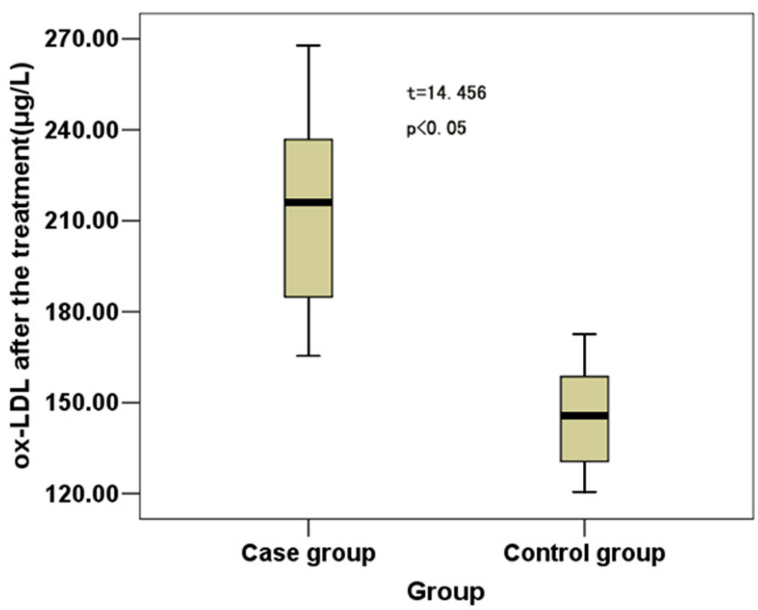

Figure 4. Distribution of serum ox-LDL level after treatment of patients in the case group and the subjects in the control group.

serum as the independent variables. After CPAP treatment, the patient's AHI level was positively correlated ($P < 0.05$) with the patient's BMI (standardized partial regression coefficient = -0.457), neck circumference (standardized partial regression coefficient = 0.669), SBP level after treatment (standardized partial regression coefficient = 0.492), serum AGEs level after treatment (standardized partial regression coefficient = 0.651), and serum ox-LDL level after treatment (standardized partial regression coefficient = 0.613) as shown in **Table 3**. After CPAP treatment, the LSaO2 of OSAHS patients was negatively correlated with patient's BMI (standardized partial regression coefficient = -0.415), HOMA index after treatment (standardized partial regression coefficient = -0.336), serum AGEs level after treatment (standardized partial regression coefficient = -0.528), and serum ox-LDL level after treatment (standardized partial regression coefficient = -0.611) as shown in **Table 4.**

Discussion

AGEs are stable compounds produced by the serial reactions between the free amino groups of macromolecular substances such as proteins, lipids, or nucleic acids and aldehyde groups under the non-enzymatic conditions. Research has shown that AGEs play an important role in the incidence and development of multiple diseases and in the aging process [4]. Studies have verified that the production and accumulation of AGEs is the core link that induces the insulin β cell functional disorder; therefore, it plays an important role in the pathogenesis of diabetes [5]. AGEs work with Toll-like receptors and activation nuclear factor-κB to induce a cascade of metabolic reactions which further promote the development of chronic inflammatory reactions in diabetic patients [6] and lead to the occurrence of various diabetic complications. As a result, the AGE level can serve as an important

Table 2. Comparison before and after CPAP treatment: clinical indexes of OSAHS patients

Clinical indexes	Before treatment (n = 60)	After treatment (n = 60)	t value	*P* value
Insulin (mIU/L)	7.91±1.56	6.53±1.34[a]	5.198	< 0.05
HOMA index	1.88±0.53	1.35±0.32[a]	6.631	< 0.05
SBP (mmHg)	129.81±13.69	115.53±12.71[a]	5.921	< 0.05
DBP (mmHg)	82.64±8.33	75.51±7.18[a]	5.022	< 0.05
AHI (times/hour)	32.18±8.17	21.46±6.35[a]	8.025	< 0.05
$LSaO_2$ (%)	72.63±6.13	85.16±5.26[a]	-12.016	< 0.05

Note: [a]: $P < 0.05$, when compared with before treatment.

index in evaluating the risk of diabetic complications such as diabetic encephalopathy and diabetic nephropathy [7].

AGEs are also closely associated with the arterial lesions. Some study results indicate that AGEs, their receptors, and the Wnt/β-catenin signal pathway are closely associated with the transformation of vascular smooth muscle cells into osteoblast-like-cells. This transformation, the corresponding synthesis of multiple bone morphogenetic proteins, and the absence of related factors that inhibit calcification are the main routes of calcification of the tunica media of arteries [8]. AGEs can also exert influences on the shape and functions of endothelial cells, smooth muscle cells, and macrophages through the direct modification of protein, lipids, and nucleic acids. AGEs can promote the progression of atherosclerosis through changing multiple factors such as arterial wall cells, extracellular matrix, blood components, and local extracellular matrix [9, 10]. Therefore, the level of AGEs is an important marker to evaluate the risk of cardiovascular and cerebrovascular diseases.

Chronic intermittent anoxia is one of the main clinical features of OSAHS. This pathological change can lead to an increase in oxidative stress and further impair vascular endothelial functions. In addition, it can produce injuries to the vascular endothelia by inducing endothelial cell apoptosis. Oxidative stress can induce an increase in expression of adhesion molecules which can increase the affinity of inflammatory cells and endothelial cells, resulting in damage caused by inflammatory reactions. Ox-LDL is the product of the oxidation of low density lipoprotein (LDL) during oxidative stress [11-13]. Research indicates that ox-LDL can induce changes in endothelial cell structure and function through the recognition of and binding with autoreceptors and the internalization of cells. This increases the formation of foam cells, and eventually leads to the formation of atherosclerosis. It is the key factor in the formation of atherosclerotic plaques [14]. As OSAHS patients experience frequent cycles of anoxia and reoxygenation, oxidative stress reactions will repeatedly occur within the body. During this process, a large quantity of reactive oxygen species will be generated. The accumulation of reactive oxygen species will eventually result in the production of ox-LDL. Therefore, the level of ox-LDL in the serum can also reflect the risk of the OSAHS patients experiencing the atherosclerotic cardiovascular and cerebrovascular diseases [15, 16].

Noninvasive mechanical ventilation is the preferred treatment for clinical OSAHS. Options include nasal intermittent positive pressure ventilation (NIPPV), CPAP, and bi-level CPAP [17]. Patients generally have good tolerance and compliance to long-term CPAP treatment. In clinical studies, some patients with ischemic heart disease complicated by OSAHS demonstrate significant improvement in heart function and structure after CPAP treatment, indicating that CPAP treatment plays an active role in the treatment of OSAHS and ischemic heart disease [18]. Other studies demonstrate that CPAP treatment has good therapeutic effects on the OSAHS patients complicated by abnormal sugar metabolism [19-21]. Therefore, the application of CPAP can not only relieve the anoxia symptoms of OSAHS patients but also exert preventive and therapeutic effects on OSAHS complicated by cardiovascular and cerebrovascular diseases through regulating metabolism.

The results of this study indicated that the levels of AGEs and ox-LDL in the serum of the patients in the case group were significantly higher than those of the control group ($P < .05$). After CPAP treatment, the serum AGE level and ox-LDL level of patients in the case group significantly dropped ($P < .05$), but were still higher than those of the control group ($P < .05$). These findings indicate that the application of CPAP

Table 3. Analysis on multi-factors that influenced the AHI level of OSAHS patients after CPAP treatment

Variables	Standard error	Standardized partial regression coefficient	t value	*P* value
BMI	0.628	0.457	6.112	< 0.05
Neck circumference	0.036	0.337	4.391	< 0.05
HOMA index after treatment	0.138	0.669	6.606	< 0.05
SBP level after treatment	0.269	0.492	5.118	< 0.05
Serum AGEs level after treatment	0.667	0.651	4.638	< 0.05
Serum ox-LDL level after treatment	0.531	0.613	5.067	< 0.05

Table 4. Analysis on multi-factors that influenced the $LSaO_2$ level of OSAHS patients after CPAP treatment

Variables	Standard error	Standardized partial regression coefficient	t value	*P* value
BMI	0.552	-0.415	-3.845	< 0.05
HOMA index after treatment	0.576	-0.537	-4.913	< 0.05
SBP level after treatment	0.691	-0.336	-6.138	< 0.05
Serum AGEs level after treatment	0.384	-0.528	-5.281	< 0.05
Serum ox-LDL level after treatment	0.267	-0.611	-4.857	< 0.05

treatment could, to varying extents, lower serum AGE level and ox-LDL level and exert oxidative stress reaction lowering and metabolism regulating effects. These reductions in oxidative stress may have the further effects of lowering the risk of the onset of cardiovascular and cerebrovascular diseases. After CPAP treatment, the clinical indexes of the patients in the case group were significantly improved when compared to pretreatment values. After CPAP treatment, the patient's AHI level was positively correlated ($P < .05$) with the patient's BMI (standardized partial regression coefficient = -0.457), neck circumference (standardized partial regression coefficient = 0.669), SBP level after treatment (standardized partial regression coefficient = 0.492), serum AGE level after treatment (standardized partial regression coefficient = 0.651), and serum ox-LDL level after treatment (standardized partial regression coefficient = 0.613). After treatment, the LSaO2 of OSAHS patients was negatively correlated with patient's BIM (standardized partial regression coefficient = -0.415), HOMA index after treatment (standardized partial regression coefficient = -0.336), serum AGE level after treatment (standardized partial regression coefficient = -0.528), and serum ox-LDL level after treatment (standardized partial regression coefficient = -0.611). These changes reveal that the application of CPAP treatment of OSAHS could significantly lower the patient's symptoms such as apnea, hypoxemia, insulin resistance, and elevation in blood pressure. The efficacy after CPAP treatment was related to the levels of AGEs and ox-LDL in the serum. The two indexes can be used to evaluate the therapeutic effect and prognosis of OSAHS patients. It should be noted that, according to related investigations, the compliance of OSAHS patients on the long-term CPAP treatment is 46% to 83%. For the patients who cannot tolerate CPAP, an oral appliance or surgical treatment is generally adopted in most cases. The oral appliance is mainly applicable to patients with simple snoring and mild OSAHS, and the surgical treatment is mainly applicable to patients without obvious upper airway anatomic obstruction. For the patients without obvious upper airway anatomic obstruction whose symptoms are not well managed by the oral appliance, improving the compliance to the long-term treatment of CPAP is currently the only option [22]. Therefore, while confirming the efficacy of short-term CPAP treatment, the clinicians should also improve the patient's compliance to the long-term CPAP treatment to achieve the targets of improving therapeutic effects and improving the patient's prognosis.

In conclusion, OSAHS patients manifest elevations in serum AGE level and ox-LDL level. Application of CPAP treatment can, to varying extents, lower the serum AGE level and ox-LDL level and exert oxidative stress reaction lowering and metabolism regulating effects. These benefits may lower the risk of the onset of cardiovascular and cerebrovascular diseases.

Disclosure of conflict of interest

None.

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