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Original Article

Prognostic role of advanced glycation end products in male patients with obstructive sleep apnoea syndrome and hypertension

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Abstract: Increased advanced glycation end products (AGE) levels have been reported in diabetes mellitus, obstructive sleep apnoea syndrome (OSAS) or hypertension patients. However, it remain unclear its prognosis value in OSAS patients with hypertension. In this study, we tried to explore the role of AGE in prognosis of OSAS patients with hypertension. 68 male OSAS patients (27 patients with hypertension, 41 patients without hypertension), 19 male control subjects were admitted. The major cardio-cerebral vascular event (MACCE) in OSAS patients were recorded in the 24-months' follow-up. There was no significant difference in ages, BMI, pack-years of smoking between, neck circumference and abdominal circumference in the three groups. The AHI and serum AGE levels of OSAS patients with hypertension were both significantly higher than controls group and OSAS without hypertension group. Moreover, the MACCE subjects were older and had higher levels of cholesterol and hs-CRP when comparing with non-MACCE subjects in OSAS patients. The MACCE subjects also had lower levels of lowest SpO_2, higher levels of AHI and serum AGE as compared with non-MACCE subjects. Serum AGE levels was negatively associated with lowest SpO_2, and positively correlated with AHI as well as hs-CRP. Multiple logistic regression analysis showed that serum AGE levels, AHI and lowest SpO_2 were independently associated with MACCE in 24 months. So, we concluded that serum AGE played a prognostic role in patients with OSAS and hypertension.

Keywords: Advanced glycation end products (AGE), obstructive sleep apnoea syndrome (OSAS), hypertension

Introduction

Obstructive sleep apnea syndrome (OSAS) is characterized by repeated periods of complete or partial collapse of the upper respiratory tract during sleep, which resulting in apneas or hypopneas [1]. These could lead to frequent awakenings and often caused daytime sleepiness. OSAS patients often presented with one or more complications, such as dyslipidemia, glucose intolerance or diabetes, coronary heart disease and hypertension [2]. Plenty of previous studies have reported the correlation of OSAS and hypertension. 20%-40% of individuals with hypertension have been subsequently diagnosed with complication of OSAS [3, 4]. Moreover, lots of reports also demonstrated the prevalence of hypertension in OSAS ranged from 22.8% to 55.6% [5, 6].

Advanced glycation end-products (AGE) are the result of oxidation reactions and non-enzymatic glycation of amino groups of proteins and reducing sugars. AGE accumulation has been recognized as factors in the pathogenesis of diabetic complications because of their highly cross-linked nature [7, 8]. AGE was also proved playing role in nondiabetic chronic diseases with systemic inflammation or oxidative stress. Recent studies have also demonstrated the increasing of AGE levels in COPD, chronic kidney disease and cardiovascular diseases [9-11]. AGE levels of serum and skin were both higher in COPD patients than controls. Accumulation of AGE was increased in patients with chronic kidney disease, particularly in those with diabetic nephropathy. Inhibition of AGE formation attenuates progression of atherosclerosis and renal injury induced by high-fat diet in Apoe-null mice.

Systemic AGE levels were also significantly higher in OSAS or hypertension patients [12-17]. Serum AGEs were increased in OSA sub-

jects as compared with control. In the subjects with OSAS, serum AGEs correlated with the duration of nocturnal desaturation, the apnea-hypopnea index (AHI) and oxidative stress levels. These associations were independent of age, sex, body mass index, smoking status, and glucose. Continuous positive airway pressure treatment could lower the serum AGE levels and benefit to sleep apnoea in OSAS patients. In hypertension population, plasma AGE concentration is significantly higher than in normotensive subjects. Furthermore, plasma AGE levels was significantly correlated with arterial wave reflections and associated with arterial stiffness in an age-dependent manner. AGE levels are associated with pulse pressure and increased aortic pulse wave velocity in adults.

However, it remains unclear the prognostic role of AGE in OSAS patients with hypertension. So, in this study we detected the serum levels of AGE and its relation with cardio-cerebral vascular events in OSAS patients with hypertension.

Materials and methods

Subjects and polysomnography

Chinese males aged 40-70 years, admitted to the Sleep Centre at Yidu Central Hospital of Weifang for diagnostic polysomnography (PSG) between October 2010 and June 2012, and were recruited in this study. Those with diabetes mellitus were excluded from the study. This study was approved by the Ethics Committee of Yidu Central Hospital of Weifang. Written informed consent was obtained from all participants.

All study participants were admitted for an overnight 16-channel PSG (Alice LE, Philips Respironics Inc., California, USA) as described previously [18]. PSG recordings were scored manually according to standard criteria. Apnea was defined as complete cessation of air flow for more than 10 s. Hypopnea was defined as a reduction of air flow more than 50%, or a reduction of air flow less than 50% but accompanied by decrease in oxygen saturation more than 3%. Measurements of apnea-hypopnea index (AHI, the total number of apnea and hypopnea episodes divided by hours of sleep) during the night were obtained. Other parameters were also recorded, including mean SpO_2, lowest SpO_2 and ESS. Subjects with tumor, hepatic, renal or inflammatory diseases were excluded. We also excluded subjects who received glucocorticoids, antiobesity, or lipid-lowering drugs.

MACCE

In admission, the data of all subjects were collected, including age, body mass index (BMI), smoking status, brachial systolic blood pressure (SBP) and brachial diastolic blood pressure (DBP). In the 2 years' follow-up period, all major cardio-cerebral vascular events (MACCE) were recorded in OSAS patients. MACCE was defined as hospitalization for myocardial infarction, unstable angina, cardiac insufficiency, cardiac arrest, stroke, or peripheral arterial event. If the OSAS patient had no MACCE in the 2 years' follow-up period, he was classified into non-MACCE group.

Laboratory detection

The blood samples were collected within 24 h after hospitalization for measurement of cholesterol, triglycerides, glucose, high sensitive C reactive protein (hs-CRP) and serum AGE. Blood samples were centrifuged with 1000 g/min for 15 min, and then the serum were separated and stored under -80°C. Plasma AGE concentration was measured by the enzyme-linked immunosorbent assay method (AGEs ELISA Kit, Cusabio Biotech, Wilmington, DE) according to instructions.

Statistical analysis

Descriptive data are presented as mean (± SD) or median (range). Comparisons between the three groups (control, OSAS with hypertension, OSAS witout hypertension) were made by using the analysis of variance (ANOVA, for continuous variables) or X^2 test (for categorical variables). Pearson correlation analyses were used to determine the relationship between serum AGE levels and other variables. Single variation analysis was performed in the comparison between MACCE patients and non-MACCE patients. After the single variation analysis between two group, all the factors with significant difference ($P<0.05$) were listed as the adjusted factors. Some other factors were also listed as the confused factor if they have been proved affecting AGE levels, such as age and smoking. Multiple logistic regression analyses were performed to test whether serum AGE

Table 1. Demographic and clinical characteristics of subjects

	Control	OSAS without hypertension	OSAS with hypertension
N	19	41	27
Age (yrs)	47.45±8.37	48.08±7.14	50.26±7.45
BMI (kg/m^2)	24.48±1.66	24.77±1.51	25.35±1.33
Pack-years of smoking	15.34±2.69	14.18±2.87	16.19±2.74
Neck circumference (cm)	36.71±4.36	38.34±4.73	39.28±5.15
Abdominal circumference (cm)	92.24±11.63	96.47±12.27	97.65±12.56
Cholesterol (mmol/L)	4.55±0.35	4.73±0.42	5.43±0.45[a]
Triglycerides (mmol/L)	2.01±0.28	1.93±0.21	2.06±0.37
Glucose (mmol/L)	4.43±0.57	4.58±0.47	4.83±0.58
Systolic BP (mmHg)	118.56±14.62	123.56±18.74	148.70±21.48[a,b]
Diastolic BP (mmHg)	73.89±10.39	75.63±10.37	97.35±11.62[a,b]
Mean SpO_2 (%)	97.62±7.26	92.53±8.78	90.36±10.29
Lowest SpO_2 (%)	93.64±8.41	79.26±8.41	71.56±8.34[a,b]
ESS	4.46±0.34	12.46±0.95[a]	14.15±1.14[a]
AHI (events/h)	3.65±0.42	37.55±4.62[a]	48.73±5.86[a,b]
hs-CRP (mg/L)	3.32±0.35	4.25±0.61[a]	6.96±0.77[a,b]
AGE (μg/ml)	0.13±0.01	0.35±0.05[a]	0.59±0.09[a,b]

[a]P<0.01 as compared with control, [b]*P*<0.05 as compared with OSAS without hypertension.

Table 2. Comparison of clinical and laboratory data between MACCE group and control group during index hospitalization

	non-MACCE group	MACCE group	*P* value
N	52	16	NS
Age (yrs)	45.65±5.37	54.83±6.26	<0.001
BMI (kg/m^2)	26.89±2.45	28.14±2.35	0.25
Pack-years of smoking	15.49±2.52	15.97±2.17	0.42
Cholesterol (mmol/L)	4.55±0.54	5.34±0.68	0.004
Triglycerides (mmol/L)	1.87±0.26	2.11±0.32	0.27
Glucose (mmol/L)	4.37±0.34	4.92±0.48	0.46
hs-CRP (mg/L)	4.52±0.54	6.68±0.57	<0.001
Mean SpO_2 (%)	93.41±10.56	89.46±11.26	0.15
Lowest SpO_2 (%)	81.58±7.41	70.14±7.35	<0.001
ESS	13.28±1.07	13.88±1.67	0.74
AHI (events/h)	34.27±5.62	52.45±5.58	<0.001
AGE (μg/ml)	0.33±0.05	0.65±0.07	<0.001

were independently associated with MACCE. Two-sided *P* value of 0.05 was considered statistically significant. All of the statistical analyses were performed using a statistical software package (SPSS 15.0).

Results

Demographic characteristics of all subjects

The demographic characteristics of subjects were shown in **Table 1**. There was no significant difference in ages, BMI and pack-years of smoking, neck circumference, abdominal circumference, serum triglycerides and glucose levels between the three groups. The levels of systolic blood pressure (SBP) and diastolic blood pressure (DBP) in OSAS with hypertension group were both significantly higher than OSAS without hypertension group and control group. Serum levels of cholesterol in OSAS with hypertension group were significantly higher than other two groups. There was no significant difference in mean SpO_2 between the three groups, but the lowest SpO_2 in OSAS with hypertension group was significantly higher than other two groups. Furthermore, the AHI, ESS, serum levels of hs-CRP and AGE in OSAS with hypertension group were all significantly higher than other two groups.

Comparison of clinical and laboratory data between MACCE subjects and control

In 24 months follow-up period, 8 patients (11.76%) died. The etiologies for death as stated on the hospital records were acute myocardial infarction (n=2), heart failure (n=1), cerebral hemorrhage (n=3) and sudden death (n=2). The differences in main parameters between MACCE subjects and non-MACCE subjects are listed in **Table 2**. There were no significant differences in BMI, pack-years of smoking, triglycerides and glucose levels, ESS and mean SpO_2 between the two groups. The MACCE subjects were older than controls (45.65± 5.37 vs. 54.83±6.26 45.65±7.37, P<0.001).

Table 3. Associations with serum levels of AGE

Criteria	r	*P* value
AHI	0.42	0.016
Lowest SpO_2	-0.36	0.025
hs-CRP	0.33	0.031

Table 4. Risk factors for MACCE in OSAS patients

	β	Odds ratio	Confidence interval 95%	*P* value
Age	0.32	1.05	0.84-1.26	0.15
Smoking	0.25	1.62	0.65-2.73	0.37
Cholesterol	0.46	1.37	0.86-1.72	0.12
Lowest SpO_2	0.89	1.74	1.24-2.47	0.01
AHI	0.71	1.48	1.17-2.15	0.03
hs-CRP	0.07	1.25	0.59-2.83	0.64
AGE	1.33	1.53	1.13-1.92	0.005

The MACCE subjects had higher levels of cholesterol and hs-CRP when comparing with controls (4.55±0.54 vs. 5.34±0.68, P=0.004; 4.52±0.54 vs. 6.68±0.57, P<0.001). Although there was no significant difference in mean SpO_2 levels between the two groups, the lowest SpO_2 levels in MACCE subjects were significantly lower than controls (81.58±7.41 vs. 70.14± 7.35, P<0.01), and the AHI levels in MACCE subjects were significantly higher than controls (34.27±5.62 vs. 52.45±5.58, P< 0.001). The AGE levels in MACCE subjects were also significantly lower than controls (0.33±0.05 vs. 0.65±0.07, P<0.001). Moreover, the results of linear correlation analysis showed that serum AGE levels was positively correlated with AHI (r=0.42, P=0.016) and hs-CRP (r=0.33, P=0.031) in OSAS patients **Table 3**. Serum AGE levels was negatively correlated with lowest SpO_2 (r=-0.36, P=0.025).

AGE and MACCE incidence

During 2-year follow-up, there were 5 cardiovascular deaths, 6 nonfatal coronary events (3 myocardial infarctions, 3 hospitalizations for unstable angina or heart failure) and 9 nonfatal strokes. A total of 4 patients experienced more than one MACCE. Multiple logistic regression analysis showed that serum AGE levels (odds ratio=1.53, 95% CI [1.13-1.92], *P*=0.005), AHI (odds ratio=1.48, 95% CI [1.17-2.15], *P*= 0.036) and lowest SpO_2 (odds ratio=1.74, 95% CI [1.24-2.47], *P*=0.01) were independently associated with MACCE in 24 months **Table 4**.

Discussion

In this study, our results showed in OSAS patients with hypertension a higher serum AGE levels which was correlated with AHI, lowest SpO_2 and hs-CRP. Moreover, OSAS patients with a higher serum AGE levels might get a higher risk of MACCE. However, it still needs a more large-scale population and a longer follow-up.

AGE is implicated in the blood and tissues of diabetic subjects as a result of hyperglycemia. Recent reports showed that AGE was formed not only in conditions of hyperglycaemia but also in states of enhanced oxidative stress, including COPD and OSAS patients [12-14]. In this study, AGE levels were significantly higher in patients with OSAS than in controls. Serum AGE levels were not only associated with AHI, but also correlated with lowest SpO_2. This is in agreement with the previous papers published on this subject [12-14], which have showed that serum AGE was correlated with the duration of nocturnal hypoxemia and AHI. These associations were independent of age, sex, body mass index, smoking status, and glucose.

Furthermore, our results also showed the association of AGE and hs-CRP, which was a critical marker of systematic inflammation. These results indicated the potential correlation of AGE with hypoxia and systematic inflammation, which were two important factors in the development of OSAS, COPD and atherosclerosis. OSAS is a widespread sleep-related respiratory disorder, characterized by repetitive episodes of complete or partial obstruction of airflow in the upper airway during sleep. Many studies have reported that OSAS is associated with reactive oxidative stress [20-22]. OSAS patients have increased levels of reactive oxygen metabolites in the blood that may result in cellular damage [20-22]. Recently, many reports have demonstrated the relation of AGE and reactive oxidative stress in diabetes and retinopathy [23, 24]. So, it is not surprise that serum AGE levels increased not only in COPD and atherosclerosis patients, but also elevated in OSAS patients.

Large-scale epidemiological studies have clearly shown that untreated OSA is an independent

cardiovascular (CV) risk factor. Amongst others, severe OSA can contribute to the emergence of arterial hypertension, heart failure, stroke, and pulmonary hypertension [25-27]. Plenty of previous studies have reported the relation of OSAS and hypertension [28, 29]. The Wisconsin Sleep Cohort Study had showed that the odds ratio for the presence of hypertension in OSAS patients after 4 years of follow-up was 1.42 to 2.89 compared with control, after adjustment for several covariates including body mass index [27]. In our study, there were 27 patients accompanying with hypertension in total 68 OSAS patients. The OSAS patients with hypertension showed a lower level of lowest SpO_2, and higher levels of hs-CRP and AHI. These indicated severe hypoxemia, inflammation and oxidative stress in these patients. Based on data obtained in patients with OSAS, it is currently believed that sympathetic activation, inflammation and oxidative stress play major roles in the pathophysiology of OSA-related CV diseases [30-32]. As such, OSAH is accepted as a cause of hypertension by both European and American clinical practice guidelines.

Previous studies have demonstrated that hypertension patients got a higher serum AGE levels when compared with control [15-17]. The aortic stiffness is strongly associated with the plasma AGE. Our result was agreed with these previous reports. Moreover, our results indicated the positive association of MACCE incidence in OSAS patients with hypertension. This might show the potential role of AGE in prognosis of hypertension patients. In the vessel wall, AGE formation may contribute to endothelial dysfunction and vascular stiffening [15-17, 33, 34]. AGE levels could represent accumulated oxidative stress during the progression of diseases, and their measurements would be useful for stratification of the cardiovascular risks [15-17, 33, 34]. So, these might explain the prognosis role of AGE in hypertension patients. However, our results did not demonstrate the long-term prognosis value of AGE in OSAS and hypertension patients as the follow-up was only 2 years. In addition, it was unsure whether serum AGE played a similar predict role in OSAS patients prognosis.

Although many reports demonstrated that elevated AGE levels were associated with OSAS, hypertension, diabetes and cardiovascular diseases, its precise mechanism remain unclear. Some previous reports might provide some indication. A study showed that accumulation of AGE in OSA may lead to diminution in early EPC (CD133+) and endothelial repair capacity over time, thus contributing to vascular pathogenesis [35]. In diabetes patients, the excessive accumulation of AGEs underlies various complications, such as diabetic vasculopathy, neuropathy, nephropathy, and retinopathy [36, 37]. AGEs may contribute to these pathologic processes by permanent chemical modification of tissue and circulating cells and proteins, or by stimulating cellular responses through receptors specific for AGE-modified proteins. However, the precise role of AGE in OSAS and hypertension is still unknown. A further study might help us uncover these.

In conclusion, our study proved the higher serum AGE levels in patients with OSAS and hypertension. Furthermore, the serum AGE levels was positive related with MACCE incidence in a 2-years follow-up. This result indicated the prognosis role of AGE in patients with OSAS and hypertension. But, a more long-term follow-up or a larger scale admitted population might be helpful.

Disclosure of conflict of interest

None.

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