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ORIGINAL ARTICLE

Effects of obstructive sleep apnea on serum brain-derived neurotrophic factor protein, cortisol, and lipid levels

Busarakumtragul Panaree · Mekseepralard Chantana · Sukhumsirichart Wasana · Neruntarat Chairat

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Abstract
Objectives Obstructive sleep apnea (OSA) is a sleep-disordered breathing leading to vascular endothelial cells dysfunction, cognitive impairment, and abnormal lipid metabolism. serum brain-derived neurotrophic factor (BDNF) protein, cortisol, and lipid levels in OSA were investigated.
Materials and methods All middle-aged subjects including healthy individuals without signs and symptoms of apnea-hypopnea and ear nose throat (ENT) outpatients were randomly recruited and screened by overnight polysomnogram (PSG). Apnea-hypopnea index (AHI) was used as a criteria to determine subjects to enroll in this program. According to AHI, they were separated into control and OSA groups. A group of 39 OSA patients (AHI≥10 events/h) and 24 control subjects (AHI<5 events/h) were selected. Serum BDNF protein was analyzed by enzyme-linked immunosorbent assay (ELISA) from venous blood collection at 8:00 a.m. following PSG. Serum cortisol was assayed by enzyme-chemiluminescense immuno assay (ECLIA). Serum lipid profile levels were determined by enzymatic colorimetric and homogeneous method.
Results Characteristics of OSA patients and control groups including gender, age, AHI, body weight, height, and BMI showed significant differences. Serum BDNF protein, cortisol, triglyceride, and total cholesterol levels in OSA and control groups were not significantly different. High density lipoprotein-cholesterol (HDL-c) in OSA was significantly lower than that of control ($p=0.008$) while low density lipoprotein-cholesterol (LDL-c) was significantly higher than that of control ($p=0.04$).
Conclusions OSA had no significant effect on serum BDNF, cortisol, triglyceride, or total cholesterol levels while LDL-c and HDL-c levels in OSA patients compared to control were significantly different at $p=0.04$, and $p=0.008$, respectively.

Keywords Obstructive sleep apnea · BDNF · Cortisol · Triglyceride · Cholesterol · ELISA

B. Panaree (✉)
Department of Physiology, Faculty of Medicine,
Srinakharinwirot University,
Sukhumwit 23, Klongtoey Nuea, Wattana,
Bangkok 10110, Thailand
e-mail: panaree@swu.ac.th

M. Chantana
Department of Microbiology, Faculty of Medicine,
Srinakharinwirot University,
Sukhumwit 23, Klongtoey Nuea, Wattana,
Bangkok 10110, Thailand

S. Wasana
Department of Biochemistry, Faculty of Medicine,
Srinakharinwirot University,
Sukhumwit 23, Klongtoey Nuea, Wattana,
Bangkok 10110, Thailand

N. Chairat
Department of Otolaryngology, Faculty of Medicine,
Srinakharinwirot University,
Ongkarak Campus, Ongkarak,
Nakornnayok 26120, Thailand

Introduction

Sleep apnea is the transient cessation of breathing rhythm during sleep. Obstructive sleep apnea (OSA) is a major public health burden among middle-aged obese populations. OSA is more commonly found in men (4–29%) than in women (2–9%) [1]. It is characterized by repeated and/or periodic cessation of breathing during sleep due to partial or

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complete upper airway, oropharyngeal, obstruction. In addition, OSA also causes significant sleep disturbances resulting in daytime sleepiness and exhaustion which may lead to traffic accidents [2] or cognitive dysfunction, including memory, problem solving, and behavioral performance deficits [3]. Additionally, OSA and metabolic syndrome are related.

Cyclical fluctuations of arterial oxygen saturation have been observed during brief hyperventilation followed by prolonged hypoventilation in most OSA patients. Hypoxia or reoxygenation might alter the oxidative balance through the induction of excess reactive oxygen species (ROS) following ischemia or reperfusion injury. These ROS may interact with nucleic acids, lipids, and proteins, and are considered to play an important role in the development of cardiovascular diseases including hypertension and coronary artery diseases. Besides recurrent reversible obstruction of the upper airway during sleep, mucosal congestion in the airway can cause local inflammation and oxidative stress which could lead to vascular damage resulting in endothelial dysfunction [4–6]. Additionally, oxidative stress induced by chronic intermittent hypoxia in cerebral microcirculation during sleep also leads to cognitive impairment in OSA patients. Hypoxic stress caused by sleep fragmentation and frequent cerebral arousals during apneic events generally activate the hypothalamic pituitary adrenocortical (HPA) axis and the sympathetic nervous system (SNS) [7]. Sleep apnea patients have a higher level of SNS activity during wakefulness and sleep, compared to healthy controls [8]. Activation of the SNS with elevated catecholamines correlates to the severity of nocturnal hypoxias [9]. Moreover, sleep fragmentation with microarousals, as present in OSA, also activates the HPA axis [10].

Brain-derived neurotrophic factor (BDNF), a member of the neurotrophic factor family, is encoded by an immediate early response gene which responds to various external stimuli such as stress, learning, physical activity including voluntary wheel running, motorized treadmill running, swimming, and maze training, neurotransmitters and hormone. BDNF participates in neuronal transmission, neurodegeneration, neuroprotection, modulation, and plasticity including expression of hippocampal plasticity. There is evidence that peripheral blood BDNF levels are related to BDNF concentrations in the central nervous system because it readily crosses the blood–brain barrier. Circadian changes, but not seasonal changes, have an effect on serum BDNF existing as the mature form with a molecular mass of 14 kDa. Recent studies reported that BDNF may be involved in the light–dark cycle pacemaker of the central nervous system. Plasma BDNF, as well as cortisol levels, are significantly higher in the morning, with a trend of constant decrease during the day [11]. Moreover, the positive correlation between BDNF and cortisol circadian rhythm may be physiologically regulated to maintain the homeostasis of integrated cerebral activities [11]. BDNF has been shown to be an essential mediator for cognitive function and memory consolidation. Reduced BDNF levels in the human brain are associated with cognitive deficits, impaired memory performance, and depression [3]. Although sleep is essential for memory consolidation and the facilitation of learning, BDNF regulation during sleep is still not widely known. Animal data have demonstrated that rats stressed by immobilization in a restricted chamber showed a BDNF reduction [12], whereas physical activity caused a BDNF increase. The hippocampal BDNF expression largely depends on the neuronal excitation (glutamate)/inhibition (γ-aminobutyric acid, GABA) balance [13], although exogenous corticosteroid hormones seem to downregulate it [14]. In healthy controls, the serum BDNF concentration increased over the first several years, then slightly decreased after reaching the adult level [12].

Cortisol is the most prominent glucocorticoid synthesized from the cholesterol precursor in the adrenal cortex [15]. Cortisol level changes with time according to diurnal variation, having the highest level in the early morning [16]. Plasma cortisol levels are increased by the stress of infection, fever, prolonged strenuous exercise, and acute anxiety [17]. Cortisol plays a permissive role in fat metabolism. Although cortisol itself has only a slight lipolytic activity, it is necessary for epinephrine, growth hormone and other lipolytic substances to stimulate hydrolysis of stored triglycerides at maximal rates. Therefore, an excess of cortisol finally results in obesity with fat deposition in different regions of the body [17]. Bratel et al. [18] found a significant increase in fasting serum cortisol concentrations in OSA patients compared with healthy controls.

Research evidence has revealed that BDNF and cortisol have impacts on neurogenesis in the brain of all mammalian species including human. It is well established that chronically elevated cortisol levels inhibit the proliferative activity in the hippocampus [19]. Dysfunction of neuronal plasticity, neurogenesis or remodeling related to stress or increased levels of glucocorticoid hormones have been found associated with the etiology of a variety of diseases including Alzheimer's disease and mood disorders [20]. BDNF is related to the total and subcutaneous fat mass and energy metabolism in diabetic patients [21]. Subcutaneous injection of BDNF in obese diabetes mice causes significant decreases in serum non-esterified free fatty acid, total cholesterol, and phospholipids levels. This indicates that BDNF improves lipid and glucose metabolism without enlarging liver or adipose tissues [22]. Chronic administration of BDNF in the hypothalamic paraventricular nucleus significantly reverses rat obesity induced by a high fat diet. BDNF significantly reduces energy intake, body weight,

body fat, lean mass, and serum metabolic indices [23]. Recent data in animal models showed that chronic intermittent hypoxia during sleep upregulates genes of lipid biosynthesis in obese mice, resulting in hypercholesterolemia and lipid peroxidation in the liver according to the severity of the hypoxic stimulus [24]. On the other hand, as sleep is important for brain functions, alterations and or disturbances in sleep may elucidate themselves as changes in BDNF [25], and cortisol levels including lipid metabolism [26]. Therefore, the objective of this study is to investigate the effects of OSA on serum BDNF and cortisol levels, as well as lipid metabolism manifested by the levels of serum triglyceride and total cholesterol including LDL-c and HDL-c in Thai middle-aged populations.

Materials and methods

Subjects

This study was approved by the Human Ethics Committees of Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand. It was started in March 2008 and ended in December 2009. All enrolled subjects were randomly recruited. All volunteers signed informed consent. Firstly, screening of patients using standard polysomnogram (Respironics: The Alice 5 Diagnostic Sleep System Model, Europe) was conducted overnight to ensure inclusion criteria in the sleep laboratory, Department of Otolaryngology, Faculty of Medicine, Srinakharinwirot University, HRH Princess Mahachakri Sirindhorn Medical Center, Ongkarak Campus, Nakornnayok, Thailand. Apnea-hypopnea index (AHI), defined as the average number of apneas-hypopnea episodes per hour of sleep, was used as a criteria to allocate the subjects into control and OSA groups. We considered hypopnea as a reduction of airflow equal or more than 50% associated with awakening and a 4% drop in peripheral oxygen saturation. Patients who had AHI equal to or more than 10 events/h were classified as OSA group, but those who had AHI less than 5 events/h were classified as control group [27, 28]. Characteristics of the subjects including number, gender, age, AHI, body weight, height, body mass index (BMI), resting systolic blood pressure (RSBP), and resting diastolic blood pressure (RDBP) were recorded (Table 1). OSA patients enrolled in this study had developed signs and symptoms of apnea-hypopnea for approximately 3 years resulting in the chronic stage of OSA. Subjects had normal circadian rhythm or normal sleep–wake cycle. Major exclusion criteria were recent history of illness including cardiovascular, liver, or renal diseases, nightshift working, transmeridian traveling during the previous 3 months, and psychiatric disorders.

Table 1 Characteristics of all subjects

Variables of subjects	Control group	OSA group	*p* value
Sample number (*n*)	24	39	0.001
Male	24 (100%)	24 (61.5%)	
Female	0	15 (38.5%)	
Age (years)	32.3±2.4	47.2±1.6	<0.001
AHI (events/h)	1.6±0.4	22.3±4.6	0.001
Body weight (kg)	62.2±2.0	74.5±1.8	<0.001
Height (m)	1.7±1.4	1.6±1.5	0.003
BMI (kg/m^2)	21.5±0.5	28.5±0.8	<0.001
RSBP (mmHg)	118.3±2.4	138.1±2.8	<0.001
RDBP (mmHg)	77.5±2.2	84.5±1.9	0.02

Control group consisted of 24 men (n=24) and OSA group 24 men and 15 women (n=39), respectively. Data are means ± SEM

OSA obstructive sleep apnea, *AHI* apnea-hypopnea index, *BMI* body mass index, *RSBP* resting systolic blood pressure, *RDBP* resting diastolic blood pressure

Specimen collection and preparation

Six milliliters of venous blood samples were drawn from the antecubital vein of OSA patients and control group. Blood was collected at 8:00 a.m. for all subjects. Serum samples were collected from the coagulated blood after centrifugation at 1,500*g* for 10 min and stored at −80°C until used.

Determination of serum BDNF protein

Chemicals of analytical grade were purchased from BDH (UK). Each serum sample was diluted at 1:100 with sample buffer and the BDNF concentrations were determined using a sandwich ELISA (Promega, USA) following the manufacturer's protocol. Briefly, 96-well flat bottom immunoplates (Immulon, USA) were coated overnight at 4°C with monoclonal anti-BDNF antibody. After rinsing once, the wells were blocked for 1 h with the blocking buffer. The plates were rinsed again and incubated with samples or BDNF standards for 2 h. The immobilized antigen was incubated with polyclonal anti-human BDNF antibody for 2 h and the secondary antibody was detected by an additional incubation with anti-IgY peroxidase conjugate for 1 h. After a final wash, tetramethylbenzidine substrate was added into the wells and incubated for 10 min. Color development was stopped by the addition of 1 N hydrochloric acid, then the absorbance of 450 nm of each well content was measured using a Microplate Reader (Multiskan Ex, ThermoLabsystem). All incubation periods were carried out at room temperature and each wash procedure consisted of 5 individual washing of the plates unless otherwise stated. Samples were assayed in triplicate.

Determination of serum cortisol

For cortisol determination, serum samples were assayed by ECLIA following the manufacturer's instruction. Serum samples were triplicately measured by cortisol assay kit purchased from Roche, USA. Samples were pipetted into disposable steriled tubes placed inside the rack fixed in the Elecsys 2010 analyzers. The Elecsys cortisol assay makes use of a competition test principle using a polyclonal antibody specifically directed against cortisol. Endogenous cortisol in the sample liberated from binding protein with danazol competes with exogenous cortisol derivative from the test which has been labeled with Tris (2,2'-bipyridyl) ruthenium (II)-complex for the binding sites on the biotinylated antibody.

Determination of serum lipids

Serum triglycerides and total cholesterol were determined by the enzymatic colorimetric method [29, 30]. HDL-c and LDL-c were directly measured by homogeneous method [31]. All lipid profile tests were run on Dimension RXL chemistry analyzer (Dade Behring, USA).

Statistical analysis

Data were expressed as means ± SEM. Statistical analysis was done using SPSS version 11.5 for Windows (SPSS, Chicago, IL). Independent samples *t* test was used to analyze the data at 95% confident interval ($p<0.05$). The influence of gender on OSA incidence was analyzed by Chi-square test. Pearson correlations(r) was used to determine bivariate association between serum BDNF protein and cortisol levels as well as total cholesterol and cortisol levels in control and OSA patient groups. In addition, the relationship between total cholesterol and BMI included HDL-c and BMI as well as LDL-c and BMI in OSA patients were analyzed by the same method.

Results

Characteristics of OSA patients and control groups including gender, age, AHI, body weight, height, and BMI showed significant differences. The AHI of OSA patients was significantly higher than that of controls ($p=0.001$). Gender, age, body weight, height, and BMI of OSA were also significantly different from those in controls ($p=0.001$, $p<0.001$, $p<0.001$, $p=0.003$, and $p<0.001$, respectively). In addition, RSBP and RDBP in OSA patients were also significantly higher than those in controls ($p<0.001$ and $p=0.02$, respectively) (Table 1). Accidentally, subjects in control group were all male ($n=24$), but those in OSA xpatients were 38.5% female ($n=15$) and 61.5% male ($n=24$). It has been reported that serum BDNF protein level in normal human was 16.3±3 ng/ml, and those in normal male and female were 16.1±7.2 ng/ml and 16.5±7.4 ng/ml respectively [32]. In the present study, OSA patients had serum BDNF concentration at 11.22±0.46 ng/ml and serum cortisol level of 336±22 nM, compared to control groups (11.17±0.41 ng/ml and 398±31 nM, respectively). These data showed no statistical differences from control group (Fig. 1). Serum cortisol level in healthy human is 171-536 nM [33]. Our result suggested that OSA had no effect on serum BDNF protein or cortisol. In addition, OSA did not affect serum triglyceride and total cholesterol compared to the control group (Fig. 2). However, LDL-c and HDL-c levels in OSA group were significantly different from those in control group ($p=0.04$ and $p=0.008$, respectively). Expectedly, the OSA patients had higher level of LDL-c (111±5 mg/dl, $n=39$) but lower concentration of HDL-c (48±1 mg/dl, $n=39$) than the controls (95±5.85 mg/dl, $n=24$; 54±2 mg/dl, $n=24$, respectively) (Fig. 2).

Serum BDNF protein level was independent of cortisol level in either OSA patients ($r=-0.288$, $p=0.169$) or control group ($r=0.011$, $p=0.960$), respectively. There was no significant correlation between serum cortisol and total cholesterol levels in either OSA patients ($r=-0.006$, $p=0.971$) or control subjects ($r=0.090$, $p=0.674$). Additionally, the total cholesterol level of OSA and control groups showed no significant correlation with BMI ($r=0.145$, $p=0.446$ and $r=0.207$, $p=0.331$, respectively). Neither serum HDL-c nor LDL-c in OSA patients and control subjects had significant correlation with the BMI values ($r=-0.191$, $p=0.313$; $r=-0.009$, $p=0.963$; $r=0.188$, $p=0.379$; $r=0.131$, $p=0.541$, respectively). Although there

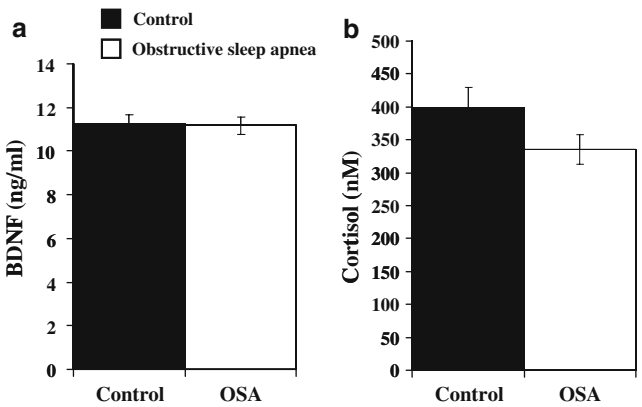

Fig. 1 **a** Means ± SEM of serum BDNF protein levels at 8:00 a.m. in control ($n=24$) and OSA groups ($n=39$), respectively. Serum BDNF protein level between both groups showed no significant difference. **b** Means ± SEM of serum cortisol levels at 8:00 a.m. in control ($n=24$) and OSA groups ($n=39$), respectively. Serum cortisol level between both groups showed no significant difference

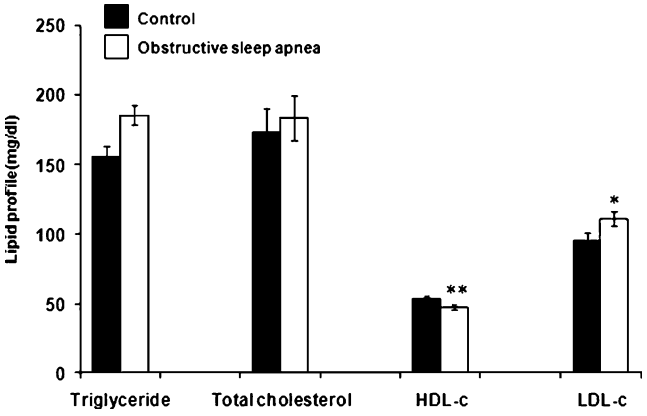

Fig. 2 Bar graphs represented means ± S.E.M. of the levels of lipid profile including serum triglyceride, total cholesterol, HDL-c , and LDL-c, respectively in control (n=24) and OSA groups (n=39). HDL-c and LDL-c levels in OSA group showed significant differences from that of control group (**p=0.008 and *p=0.04, respectively)

was no significant correlation between BMI and AHI in control (r=0.047, p=0.829), statistical correlation in OSA patients was observed (r=0.382, p=0.041). However, neither BDNF nor cortisol levels had significant correlation with total cholesterol, LDL-c, HDL-c, and AHI in both OSA and control groups (data not shown).

Discussion

This study demonstrated that OSA had an effect on the lipid profile, HDL-c and LDL-c, but not on serum BDNF protein or cortisol levels compared to control group. The characteristics of OSA group including gender, age, AHI, body weight, height, BMI, RSBP and RDBP were significantly different from those of control group. Higher incidence of OSA was observed in men (61.5%), which was supported by the study of Wahner-Roedler and colleagues [34]. The prevalence of OSA increased with aging at a rate of 11.62% [35], which was consistent with our study. Obesity is classified as BMI≥30 k g/m^2 [36]. The previous finding showed that obesity was a major risk factor for the development of OSA [37–39]. Although our OSA patients were classified as overweight, but not obese, persons, a significant BMI value was shown. It seemed that BMI had a relationship with OSA in the way that the higher the BMI of the subjects, the higher the risk of having OSA. BMI value was related to AHI [40]. Our result was consistent with recent studies [1, 40, 41] that there was a significant increase in BMI and AHI in OSA patients. Although resting blood pressure of OSA patients was significantly higher than that of control group, it was ranged in normal value at the upper border line.

AHI of PSG had a highly positive correlation with the oxygen desaturation index (ODI) of pulse oximetry [42] which was consistent with the study of Oeverland and his colleagues [43]. They showed that AHI values were more reliable than ODI. In the present study, AHI values were used instead of ODI as a diagnostic gold standard to make a differential diagnosis for OSA patients. However, the use of AHI value to represent ODI may not be accurate when there are central sleep apneas [42] or many short episodes of apneas [44] which do not result in a decrease in oxygen saturation (SaO_2). Obese patients with sleep-disordered breathing may be due to excess body weight which is prone to have more severe oxygen desaturation [45]. Moreover, the effect of excess body weight on lung volume is the principal mechanism by which BMI influences the changes in SaO_2 [46]. Börgel et al. reported that BMI had a relationship with OSA [40], and with severity of oxygen desaturation during apneas and hypopneas of sleep-disordered breathing [47]. Moreover, the progression of OSA causes the worsening epidemic of obesity [48]. In addition, the percentage of total sleep time (TST) with peripheral oxygen saturation (SpO2) <90%, an index of nocturnal hypoxia, may be a useful parameter to identify upper airway obstruction in OSA with or without obesity-hypoventilation syndrome (OHS) [49]. OSA patients with OHS always exhibit severe prolonged oxygen desaturation during sleep [50, 51]. A previous study reported that the percentage of TST with SpO2 <90% in OSA with OHS was significantly higher than that of OSA [49]. In the present study, although our OSA patients were not obese, AHI and BMI between control and OSA groups showed significant differences. Therefore, our OSA group may have significantly higher TST with SpO2 <90% than that in control group. Nevertheless, this study did not concern the result of TST with SpO2 <90% due to a limitation of data collection.

It has been reported that plasma BDNF levels decrease with increasing age in both males and females [52]. According to our middle-aged populations, that may be the reason why serum BDNF level in both control and OSA patients were lower than normal adults without a clear reason. Possibly, this may be due to the different ethnic groups. Our subjects were recruited from Thai populations, but the healthy group enrolled in the previous study were recruited from a western country, Germany [32]. Besides the age, hypoxic conditions may be related to BDNF concentration. It was reported that, in healthy young men, acute hypoxia caused an increase in serum BDNF level compared to normoxic control [53]. Moreover, Mitchell et al. [54] showed that BDNF attenuated hypoxic neurotoxicity. However, in our study, OSA with pausing in breathing during sleep did not show a difference in serum BDNF protein compared to control group. The unchanged BDNF level protein may be due to the OSA patients having only intermittent pauses in breathing, whereas the hypoxic condition lasted continuously for 30 min [53]. This

suggested that the duration of hypoxic period may affect serum BDNF concentration. The serum BDNF level in type 2 diabetes mellitus showed positive correlation with BMI, fat mass, triglyceride level, diastolic blood pressure, total cholesterol, and LDL-c levels but not with age [21, 55]. According to our data, OSA patients had significant levels of age, AHI, body weight, height, BMI, RSBP, RDBP, LDL-c, and HDL-c, but neither BDNF nor cortisol levels compared to controls. The higher level of LDL-c in OSA group may be an internalization-defect in LDL-receptor activity [56], and the lower level in HDL-c will be discussed later. Thus, BDNF may play a direct role in energy homeostasis by involving lipid metabolism in OSA patients. Additionally, significantly elevated RSBP and RDBP may be risk factors for metabolic syndromes and/or cardiovascular diseases.

Cortisol is another hormone synthesized in response to conditions such as those in OSA patients [57]. However, serum cortisol concentrations in OSA patients were not statistically different from those in control group. It is possible that the levels of both BDNF and cortisol depend on the circadian rhythm or pulsatile pattern. The present data did not investigate BDNF or cortisol levels in OSA and control subjects throughout the whole day, but they were measured once a day at 8:00 a.m., a peak period. Parlapiano et al. [58] found that OSA patients with underlying hypertension lacked cortisol circadian rhythm. OSA patients often exhibit microarousals leading to sleep fragmentation as well as sleep deprivation. Sleep deprivation is accompanied by HPA axis excitation [59]. Sleep fragmentation sometimes causes additional pulsatile cortisol release. The circadian rhythm of cortisol is affected by the final awakening time. In this study, the levels of serum BDNF protein and cortisol in OSA patients showed no significant change. There may be a negative feedback mechanism from the adrenal cortex to inhibit the HPA axis in OSA patients. The HPA axis may respond differently depending on the severity of disease, and/or the onset of diseases, acute or chronic stage. In acute OSA patients, HPA axis activity increases whereas in chronic OSA cases its activity decreases [59, 60]. Apart from the control group, only chronic OSA patients were recruited for our study. Therefore, HPA axis may be inhibited by the negative feedback mechanism resulting in downregulation of corticotropin-releasing hormone (CRH) from hypothalamus, adrenocorticotropic hormone (ACTH) from anterior pituitary gland, and cortisol from adrenal cortex, respectively.

A recent study reported that the degrees of metabolic impairment and hypercholesterolemia were dependent on the severity of the hypoxic stimulus [61]. Since cortisol is a glucocorticoid synthesized from the cholesterol precursor, its level should have a linear relationship with total cholesterol [11]. Our result showed that there was no significant correlation between total cholesterol and cortisol in either controls or OSA patients which possibly resulted from negative feedback mechanism of HPA axis [17]. The remaining total cholesterol precursor which was not used to synthesize cortisol along the HPA axis, vitamin D, progesterone, estrogen, testosterone, biliary salt, or other products, may circulate to precipitate along the vascular endothelium leading to increased risk of atherosclerosis. Besides the hypoactivity of HPA axis, chronic onset of OSA patients may have abnormal lipid metabolism with a still unknown mechanism. In our study, OSA patients had a significantly higher LDL-c level than that of the control group which was relevant to their higher BMI value. Many studies suggested that manifestations of metabolic syndrome such as hypercholesterolemia, dyslipidemia, diabetes mellitus type 2, and hypertension are a group of high risk factors causing OSA [62, 63]. Jianguo et al. [24, 61] suggested that OSA patients with the most severe respiratory disturbances are at the greatest risk to hyperlipidemia, but patients with mild to moderate OSA may exhibit increased lipid peroxidation leading to the progression of atherosclerosis. There is an inverse correlation between the HDL-c level and the incidence of coronary heart disease [64]. In the aspect of lipid profile, HDL-c, a good lipoprotein, has antioxidant and anti-atherogenic effects [64]. Lower significant level of HDL-c in OSA patients was observed in our study. In addition, Kathryn et al. [64] found that the degree of HDL dysfunction was higher in OSA patients than that in control, although similar levels of HDL were observed in both groups. These OSA patients with low concentration of HDL may lead to atherosclerosis and coronary heart disease. In the elderly, BDNF acts as a protective factor against metabolic and cardiovascular disorders [65]. However, BDNF synthesis decreases in aging.

Incidence of OSA in ageing results in a significant impairment of procedural and verbal memory [66]. The present data showed that no different levels of BDNF between OSA and control groups. This may indicate that, firstly, severity of our OSA subjects was not high enough to impair BDNF synthesis and/or function. The value of AHI>30 events/h is classified as severe OSA [67]. Secondly, OSA subjects in this study were middle-aged, not elderly.

In conclusion, OSA patients with significant differences of anthropometric characteristics, HDL-c and LDL-c levels compared to control group may be at greater risk for cardiovascular and cerebrovascular diseases, and metabolic syndromes leading to hypertension, coronary heart disease, myocardial infarction, congestive heart failure, stroke, senile dementia, type 2 diabetic mellitus, and hyperlipidemia. Therefore, suspected OSA patients should visit a physician to be investigated and have an appropriate medical treatment as soon as possible to prevent those complications. In addition,

the degree of severity of OSA may play a major role on BDNF synthesis and/or function. Therefore, this aspect is of interest for further study.

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