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Obstructive sleep apnea: Influence of hypertension on adiponectin, inflammatory markers and dyslipidemia

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ABSTRACT

Obstructive sleep apnea (OSA) is a common but often unrecognized condition with potentially serious complications. The aim of this study was to explore the possible mechanisms linking hypertension (HT), a common cardiovascular disease (CVD), with obstructive sleep apnea (OSA) by investigating the levels of morning and evening serum adiponectin, inflammatory markers (TNF-α, IL-6), and lipid profiles in OSA patients with and without HT. Four groups were enrolled in this case-control analytic study: control, OSA, OSA + HT, and HT groups, each of which included 22 subjects. The results revealed low morning and evening serum adiponectin levels in patients with OSA and OSA + HT compared with their control and HT counterparts. Serum adiponectin levels declined progressively with increasing severity of OSA. Also, morning adiponectin levels were significantly decreased at the same time that a loss of the normal diurnal rhythm was observed in the OSA and OSA + HT groups. Both TNF-α and IL-6 levels were significantly increased in the OSA and OSA + HT groups compared with levels in the control and HT groups. Altered lipid profiles was noticed in the same groups. These findings were more pronounced in the OSA + HT than in the OSA group. In conclusion, the biochemical findings of this study demonstrate predominantly low adiponectin levels, increased levels of inflammatory markers, and atherogenic lipid profiles in OSA patients with HT compared with those of the other patients studied. This highlights the possible contributing role of these factors to the pathogenesis of HT as a common cardiovascular complication in OSA patients.

1. Introduction

OSA is a common disorder affecting about 4% of middle-aged males and 2% of middle-aged females [1]. The pathophysiology of OSA is characterized by repetitive occlusions of the posterior pharynx during sleep, leading to hypoxemia and arousals. Clinically, it is characterized by intermittent snoring, witnessed apneic episodes, and daytime sleepiness [2].

The major public health burden in OSA patients is the strong risk of CVD. An independent relationship between OSA and the initiation and progression of several CVDs, particularly arterial HT, has been demonstrated [3]. The pathogenesis of cardiovascular complications in OSA is not well elucidated; however, the etiology seems to be multi-factorial in origin [4].

Adiponectin is an adipose tissue-derived hormone possessing anti-inflammatory properties that exerts a pivotal role in vascular protection through activation of multiple intracellular signaling cascades. Decreased plasma adiponectin levels were implicated in the pathogenesis of many CVDs and atherosclerosis [5].

Inflammatory processes leading to endothelial dysfunction are also postulated to play a role in the pathogenesis. The repetitive cycles of short periods of hypoxia followed by rapid reoxygenation preferentially activate inflammatory nuclear factor kappa-B (NFκB)-mediated pathways, which results in activation of inflammatory cells and release of inflammatory mediators associated with vascular pathophysiology [6].

This study was designed to explore the possible contributory mechanisms that may underlie the development of HT in OSA through evaluation of adiponectin, inflammatory cytokine TNF-α,

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and IL-6 levels, and lipid profiles in OSA patients with and without HT.

2. Subjects and methods

2.1. Study groups

Eighty-eight subjects were enrolled in this case-control analytic study. An informed written consent was obtained from all the participants and the study was approved by the Faculty of Medicine Ethics Committee, Assiut University.

Those enrolled were divided into four groups, each of which included 22 subjects, as follows:

Control group: This group included subjects who were completely healthy and free from OSA, as indicated by polysomnography (PSG) records, and from any other disease as well.

OSA group: This group included patients diagnosed with OSA based on the apnea-hypopnea index (AHI) value in their PSG records. They were free from HT.

OSA patients were further stratified into mild, moderate, and severe OSA subgroups based on AHI values during sleep [7].

- Mild OSA: Patients with AHI – more than 5/hour but less than 15/hour.
- Moderate OSA: Patients with AHI – more than 15/hour but less than 30/hour.
- Severe OSA: Patients with AHI – more than 30/hour.

OSA + HT group: This group included patients diagnosed as OSA cases by PSG with associated essential HT.

HT group: This group included patients diagnosed with essential HT. They were free from OSA based on normal PSG findings.

2.2. Clinical assessment

2.2.1. Demographic data

Age, gender, height (in meters), weight (in kilograms), and complete medical history were recorded. Attention was given to history suggestive of OSA (night symptoms: snoring, choking, and witnessed apneas; daytime symptoms: excessive daytime sleepiness). Medication use and habits were obtained. Excessive daytime sleepiness of patients was assessed according to the Epworth Sleepiness Scale (ESS), and scores more than 11 were considered pathological [8].

2.2.2. Physical assessment

Neck and waist circumferences (NC and WC; in cm) were recorded. Body mass index (BMI) was calculated as weight in kilograms obtained on a medical weight scale divided by the square of the height in meters. Blood pressure (BP) was measured with a mercury column sphygmomanometer with the subject in the supine position. Three measurements were averaged and the mean was used in the analysis. Mean arterial pressure (MAP) was calculated as diastolic pressure plus one third of pulse pressure.

2.2.3. Exclusion criteria

Patients with a known inflammatory or any other chronic disease, diabetes mellitus, cerebrovascular disease, hepatic or renal disease, cardiovascular disease other than essential HT, chronic pulmonary disease, chronic use of medication, or those who smoke were excluded from this study.

2.2.4. Polysomnography (PSG)

All subjects included in this study underwent full-night-attended PSG, using a computerized sleep system (Somnostar 4100, Sensor-Medics Co., Yorba Linda, CA, USA) at the sleep laboratory of Chest Diseases and TB Department of Assiut University Hospital. The polysomnogram systematically monitors the electroencephalogram (EEG), electro-oculogram (EOG), electromyogram of the chin (EMG), electrocardiogram (ECG), nasal and oral airflow, thoracic and abdominal efforts, pulse oximetry, and snoring sound level. Polysomnograms were all scored manually according to the American Academy of Sleep Medicine guidelines version 1.7 [7].

Apnea was defined as a complete cessation of airflow for more than 10 s. Hypopnea requires an event of at least 10 s duration in association with a >30% drop in the baseline amplitude and a >4% desaturation from the baseline saturation. The AHI was calculated as the number of apnea and hypopnea events per hour of sleep. Oxygen desaturation was defined as a drop of at least 4% below the baseline level.

2.2.5. Biochemical analysis

Two peripheral venous blood samples were drawn from all study participants: the first at 8:00 pm before performing the PSG, and a second at 8:00 am in the morning after 12 h of overnight fasting. Drawn samples were centrifuged immediately at 4000 rpm for 10 min and serum was equally divided into aliquots and stored at −20° C till assayed.

Determination of serum adiponectin (both in morning and evening samples) was done using the Assay Max Human Adiponectin ELISA Kit, Catalog No. EA2500-1, Lot No. 10011218, purchased from ASSAYPRO.USA.

TNF-α (in the evening samples) was determined using the Assay Max Human TNF-α ELISA Kit, Catalog No. ET2010-1, Lot No. 05651224, purchased from ASSAYPRO.USA. IL-6 (in the evening samples) was determined using Avi Bion Human IL-6 ELISA, purchased from Ani Biotech Oy, Orgenium Laboratories Business Unit, FIN-01720, Vantaa, Finland.

Serum lipid profiles (in the morning fasting samples), including total cholesterol (TC), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG) were estimated using a spectrophotometer analysis. Kits were purchased from the Egyptian Company for Biotechnology (S.A.E). Serum low-density lipoprotein (LDL-C) was calculated following the method of [9].

3. Statistical analysis

The results are presented as mean ± SE (standard error). All values were compared using one-way analysis of variance (ANOVA) followed by a Newman-Keuls test for multiple comparisons with $p < 0.05$ considered statistically significant. Pearson's correlation coefficient test was used to assess the correlation between parameters. Prism computer program (graph pad version 3.0) was used for the statistical analysis.

4. Results

4.1. Demographic data and BP

Table 1 shows that there was no significant difference in BMI, age, or sex among the groups studied. However, NC measurements were significantly increased in OSA and OSA + HT patients compared with those of controls ($p < 0.05$ for each) and those in the HT group ($p < 0.001$ and $p < 0.01$, respectively). A significant increase in WC measurements was also seen in the OSA and OSA + HT groups compared with those in both the control and HT groups ($p < 0.05$ for all). Mean systolic and diastolic pressures and MAP were significantly increased in the OSA + HT and HT groups compared with those in the control and OSA groups ($p < 0.001$ for all). Moreover, systolic and diastolic pressures and MAP showed a significant

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