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Original Article

Impact of obstructive sleep apnea on the 24-h metabolic hormone profile ☆

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ABSTRACT

Objective: Obstructive sleep apnea (OSA) has been associated with metabolic disorders. Sleep-disordered breathing could generate an altered rhythm in the expression of metabolic hormones, which could predispose to metabolic disorders. The aim of this study was to evaluate the effect of sleep apnea on diurnal variations in metabolic hormones.
Methods: Thirty-seven male, newly diagnosed, patients with OSA with an apnea–hypopnea index (AHI) ⩾20/h and 11 male controls (AHI <10/h) matched for body mass index (±3 kg/m^2) were included. Six different samples were obtained from each subject during a period of 24 h. Levels of the metabolic hormones ghrelin, leptin, resistin, and adiponectin were measured in plasma by immunoassay.
Results: Patients with OSA (AHI (mean ± SD) 46 ± 26/h) were older than the controls (42 ± 9 vs 33 ± 9 years, $P = 0.01$). Differences in metabolic hormones between groups did not reach statistical significance at any point in the evaluation. No significant differences were observed in the area under the curve for any of the hormones analysed. Likewise, we did not detect diurnal variations in metabolic hormones.
Conclusions: The results of this study indicate that the day–night variations in the levels of several metabolic hormones are not influenced by the presence of sleep apnea.
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1. Introduction

Obstructive sleep apnea (OSA) is a common disease that affects 3–7% of the general population [1,2]. Sleep apnea is caused by the collapse of the upper airway during sleep, which leads to transient asphyxia. These events lead to a poor quality of life, as well as metabolic disturbances. The consequences of obstructive sleep apnea (OSA) are largely mediated by chronic intermittent hypoxia and sleep fragmentation, which might contribute to the pathogenesis of cardiovascular disease described in patients with sleep apnea [3]. Obesity, a major pathogenic factor in OSA in adults, is often present [4,5]. Furthermore, OSA-related factors contribute to the development of metabolic dysregulation: OSA has been associated with hormonal and metabolic alterations that could predispose patients to obesity. As obesity often coexists with OSA, it is not yet clear whether the presence of metabolic disorders is a consequence of OSA or simply reflects the effects of coexisting severe obesity [6].

Previous studies have explored the association between OSA and alterations in the secretion of metabolic hormones [7–9]. The methodological approach of these studies included individual samples obtained at one time point. It is of potential interest to explore the effect of OSA on metabolic hormone secretion during the night, which is when most of the changes associated with chronic intermittent hypoxia and sleep fragmentation are most apparent [10]. Moreover, changes during sleep may be partly related to circadian factors, as the central and peripheral circadian clocks have been linked to both whole-body and organ-specific energy metabolism [11]. The aim of this study was to evaluate the effect of sleep apnea on diurnal variations in metabolic hormones.

☆ This study was presented in abstract form, entitled ‘Effect of sleep apnea on the 24-h metabolic hormones profile’, at the American Thoracic Society Conference 2011, Denver, Colorado, USA, 13–18th May 2011.

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2. Methods

2.1. Subjects and ethics

We studied 37 male patients with OSA (apnea–hypopnea index (AHI) ⩾20/h) and 11 males without OSA (AHI <10/h) as a control group. All participants were referred by primary care physicians for evaluation of suspected OSA and were studied in the Sleep Unit of our institution. No participant had been previously diagnosed as having OSA. Each participant was interviewed and informed in detail about the purpose of this study. The subjects were matched for body mass index (BMI; ±3 kg/m^2) and waist circumference (±5 cm), and none of them had been involved in night-shift work or transmeridian travel, or had recently lost or put on weight. The diagnosis of OSA was established by full polysomnography (E-Series Compumedics, Abbotsford, Australia), including recording of oronasal flow and thoraco-abdominal movements, electrocardiography, sub-mental and pre-tibial electromyography, electro-oculography, electroencephalography, and transcutaneous measurement of arterial oxygen saturation (SaO_2). Apnea was defined as an absence of airflow for >10 s. Hypopnea was defined as any airflow reduction that lasts >10 s and results in arousal or oxygen desaturation. Desaturation was considered to be a decrease in SaO_2 ⩾4%. The AHI was defined as the sum of the number of apneas plus hypopneas per hour of sleep.

No participant suffered from any chronic disease (diabetes, hypertension, chronic obstructive pulmonary disease, liver cirrhosis, thyroid dysfunction, rheumatoid arthritis, chronic renal failure, and/or psychiatric disorders), or was taking any type of medication. The Ethics Committee of our institution approved the study, and all the participants signed their consent after being fully informed of its goal and characteristics. The analysis of day–night variations in the endothelial dysfunction markers and haemostatic factors of the subjects included in the present study has been previously published [12].

2.2. Twenty-four-hour repeated blood sampling protocol

The participants arrived at the sleep unit of our institution at 21:00, after fasting for ⩾6 h. They all received a 24 h standard isocaloric intake (2200 kcal) (Health and Human Services/US Department of Agriculture Dietary Guidelines 2010 for non-active men aged 31–50 years) to maintain the body weight registered on admission. The subjects ate four meals a day, distributed as shown in Fig. 1. They were exposed to light from 21:00h to 23:00h and from 7:00h to 18:00h and were studied in bed in the dark from 23:00h to 7:00h, as they slept. A heparinized venous catheter (Introcan Safety®; Braun, Melsungen, Germany) was inserted into an antecubital vein to allow serial blood sampling to take place throughout the night without disturbing sleep. Six different samples (20 mL each) were obtained from this catheter over the next 24 h (10:00, 02:00, 06:00, 10:00, 14:00, 18:00) (Fig. 1). Blood was collected in tubes containing EDTA (10 mL). The sample obtained at 10:00 was followed by an additional sample (10 mL) collected in tubes with no anticoagulant, for general biochemical assessment. Blood samples were immediately processed and centrifuged for 15 min at 2500 rpm (Jouan SA, model CR4 22, Saint-Herblain, France). Serum and plasma were frozen at −80 °C until analysis.

The participants remained in the hospital for the entire study. During the day, they were allowed to rest or to perform tasks involving little activity.

2.3. Biochemical analysis and enzyme-linked immunosorbent assays

Glucose, cholesterol, triglycerides and high-sensitivity C-reactive protein were measured in serum using standard automated

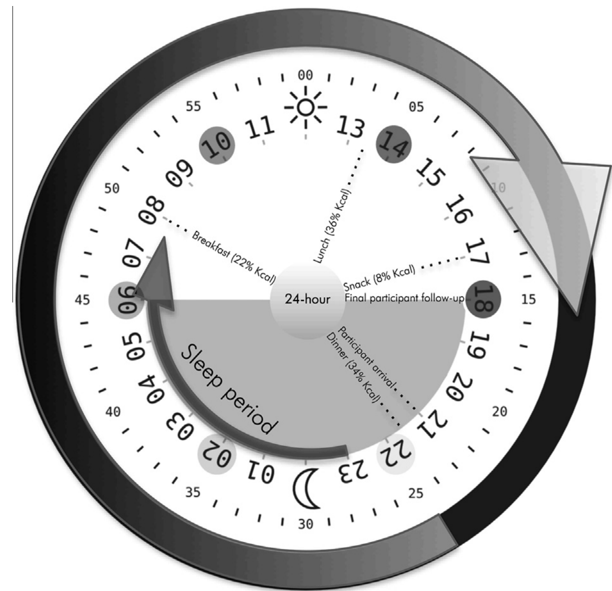

Fig. 1. Interventions for each patient in a 24 h cycle. For each study participant: 21:00h; participant arrives at sleep unit. 21:30h; dinner (34% calories). 22:00h; first blood sample collection. 23:00h-7:00h; sleep period. 14:00h; second blood sample collection. 18:00h; third blood sample collection. 8:00h; breakfast (22% calories). 10:00h; fourth blood sample collection. 13:30h; lunch (36% calories). 14:00h; fifth blood sample collection. 17:00h; snack (8% calories). 18:00h; Sixth blood sample collection. End of participant's follow-up. The patient leaves the hospital sleep unit.

enzymatic methods on a Hitachi 917 biochemical analyser (Roche Diagnostics, Indianapolis, IN, USA). High-density lipid (HDL) cholesterol was measured by a homogeneous, enzymatic colorimetric method, using a commercial reagent set (Roche Diagnostics). Low-density lipid (LDL) cholesterol concentration was calculated using the Friedewald equation. High-sensitivity C-reactive protein (hs-CRP) was measured using a chemiluminescent immunometric assay (Immulite 2000, Siemens Healthcare Diagnostics, Inc., Tarrytown, NY, USA). For hs-CRP the assay range was 0.2–100 mg/L, and the sensitivity was 0.2 mg/L. For mean levels of 0.85 mg/L the coefficients of variation (CV) were: 4.7% for CV intra-assay, and 7.1% for CV inter-assay. Resistin, total ghrelin (both intact and des-octanoyl forms), leptin, and adiponectin levels were determined in plasma EDTA by enzyme-linked immunosorbent assay, using commercially available kits. All the measurements were performed in duplicate and the mean values were used for analysis. For leptin (Millipore Corp., Saint Charles, MO, USA; Cat. #EZHL-80SK), the assay range was 0.5–100 ng/mL, and the sensitivity was 0.5 ng/mL. For mean levels of 11.26 ng/mL, the CV was 1.4% intra-assay, and 1.7% inter-assay. For ghrelin (Millipore Corp., Cat. #EZGRT-89K), the assay range was 50–5000 pg/mL, and the sensitivity was 50 pg/mL. For mean levels of 868.4 pg/mL, the CV was 1.11% intra-assay and 5.18 inter-assay. For adiponectin (Millipore Corp., Cat. #CYT350), the assay range was 100–6400 ng/mL and the sensitivity was 10 ng/mL. For mean levels of 5900 ng/mL the CV was 3.84% intra-assay and 5.5% inter-assay. For resistin (Invitrogen Corp., Camarillo, CA, USA; Cat. #KHP0051), the assay range was 2.5–20 ng/mL and the sensitivity was 0.1 ng/mL. For mean levels of 5.19 ng/mL the CV was 3.77% intra-assay and 6.8% inter-assay.

2.4. Statistical analysis

The sample size was established with reference to similar studies in which metabolic hormone levels were evaluated but only at specific time-points, some studies being in populations with different characteristics to the population of this study [13–15]. The

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