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Effects of obstructive sleep apnea syndrome on hepatic steatosis and nonalcoholic steatohepatitis

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Abstract

Hepatic steatosis occasionally progresses to nonalcoholic steatohepatitis. This study was designed to examine whether non-obese patients with obstructive sleep apnea-hypopnea syndrome (OSAHS) were prone to develop hepatic steatosis and whether repeated hypoxemia contributed to the progression of steatohepatitis.

This study included 83 OSAHS patients and 41 age-, body mass index (BMI)- and gender-matched non-OSAHS patients diagnosed by polysomnography. Hepatic steatosis was defined by a liver/spleen ratio <0.9 on abdominal computerized tomography, and latent steatohepatitis was evaluated based on serum levels of type III procollagen (P-III-P).

Visceral fat (V-fat) accumulated much more in OSAHS patients. Liver/spleen ratios in OSAHS patients correlated negatively with BMI and, especially, with the amount of visceral fat. Serum levels of P-III-P in OSAHS patients correlated negatively with the average of oxygen saturation during sleep, and positively with BMI, the apnea-hypopnea index (AHI) and the amount of V-fat. Multiple regression analysis showed that average SaO_2 was the only explanatory variable for P-III-P values, but AHI, BMI and V-fat was not.

These observations confirmed that non-obese patients with OSAHS are at a risk for visceral obesity, and suggested that oxygen desaturation during sleep is a risk for developing latent steatohepatitis, especially in patients with substantial hepatic steatosis.

Keywords: Obesity; Hypoxemia; Type III procollagen; Liver fibrosis

1. Introduction

Obstructive sleep apnea-hypopnea syndrome (OSAHS) attracts much attention because of emerging data on important cardiovascular sequelae [1,2]. Obesity, male sex, and older age are recognized to be risk factors for OSAHS and obesity is known to play a major role, because many patients with this disorder are obese and obesity is the only reversible risk factor of importance [3]. In addition, obstructive sleep apnea has been shown to be associated with visceral fat accumulation [4] and thereby the risk of obesity-related disorders. Simultaneous presence of obesity and OSAHS could increase cardiovascular complications.

Obesity is also recognized as a risk factor for developing hepatic steatosis [5] and hepatic steatosis, irrespective of its etiology, could be the first step in the pathogenesis of steatohepatitis [6]. Alcohol is a well-established cause of steatohepatitis, but steatohepatitis with necroinflammation, liver fibrosis and even cirrhosis could also be induced by nonalcoholic factors (nonalcoholic steatohepatitis, NASH) [7]. The “two-hit theory” is proposed to explain the development of NASH, in which a “second hit” capable of inducing hepatocytes necrosis, inflammation, and fibrosis is indispensable in addition to simple steatosis [8].

A case of NASH with Pickwickian syndrome, also known as obesity-hypoventilation syndrome, was reported [9]. Hypoxemia associated with that syndrome, which could

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accelerate hepatocytes destruction, was proposed as a factor contributing to the progression of liver fibrosis since hepatocytes are very susceptible to hypoxia [10]. One of the features of OSAHS in Japan is that about 30% of the patients are non-obese [3], and the pathophysiological characteristics of this subgroup of patients have not been defined. In addition, in non-obese patients OSAHS may represent an initial stage of hepatic steatosis. Therefore, in this study, the association between non-obese (body mass index (BMI) ≤ 30) OSAHS and visceral fat accumulation, hepatic steatosis and steatohepatitis were investigated.

2. Methods

2.1. Patients

The study population consisted of 83 non-obese (BMI ≤ 30) patients with OSAHS and 41 without OSAHS. No statistically significant difference was observed between these two groups regarding age, body mass index or gender. OSAHS was diagnosed based on the findings of polysomnography (PSG). Individuals with excessive alcohol consumption (>20 g/day) and those with hepatitis virus B and/or C were excluded by systematic history taking and blood tests, since this study was designed to examine the association between OSAHS and hepatic abnormalities. All patients were free from heart failure, or other respiratory problems, including chronic obstructive pulmonary disease at the time of PSG.

2.2. Polysomnography

Participants were asked to complete a questionnaire on sleep symptoms, medical history and medications. OSAHS was established on the basis of clinical and polysomnographic criteria. The apnea-hypopnea index (AHI), that is the average number of episodes of apnea and hypopnea per hour of sleep, was calculated as the summary measurement of sleep-disordered breathing. In addition to clinical symptoms, an AHI of more than 5 events/h was also used as a selection criterion. The study protocol was approved by the Research Ethics Committee of Chiba University School of Medicine, and all patients gave their informed consent prior to the study.

Overnight PSG (Compumedics, Melbourne, Australia) was performed between 9:00 p.m. and 6:00 a.m. The PSG consisted of continuous polygraphic recording from surface leads for electroencephalography, electrooculography, electromyography, electrocardiography, thermistors for nasal and oral airflow, thoracic and abdominal impedance belts for respiratory effort, pulse oximetry for oxyhemoglobin level, tracheal microphone for snoring, and sensor for the position during sleep. PSG records were staged manually according to standard criteria [11]. Respiratory events were scored according to AASM criteria [12]. Severity of OSAHS was determined by the AHI and the mean oxygen saturation (SaO_2) during sleep.

2.3. Laboratory tests

At 7:00 a.m. on the morning after the sleep study, venous blood was obtained in the fasting state to measure levels of AST, ALT, triglycerides (TG), fasting plasma glucose (FPG) and type III procollagen (P-III-P).

2.4. Radiological assessment

The amount of abdominal and visceral fat (V-fat) deposition was assessed by the computerized tomographic (CT) method. The area of the subcutaneous fat (S-fat) and visceral fat was measured in a single cross-sectional scan at the level of the umbilicus. An image histogram was computed for the subcutaneous fat layers in order to determine the range of CT numbers for the fat tissue. The total fat area was then calculated by counting the pixels that had intensities within the selected range of CT numbers. The intraperitoneal space was defined by tracing its contour on the scan image. The total area with the same CT numbers was considered to represent the visceral fat area. Subtraction of the visceral fat area from the total fat area was defined as the subcutaneous fat area [13]. V/S ratio was calculated as VFA was divided by amount of SFA. Patients were diagnosed as having hepatic steatosis when the L/S ratio was less than 0.9 [14–16].

2.5. Statistics

The results were expressed as mean values $\pm$ standard errors. The Mann–Whitney *U*-test was used to compare age, BMI, serum parameters, sleep parameters and CT parameters between patients with and without OSAHS. Proportions were compared with the chi-squared test. Linear regression analysis was performed to examine the association of two parameters. Multiple regression analysis was performed with P-III-P values as the dependent variables and AHI, average of SaO_2 during sleep, BMI and area of V-fat as explanatory variables. *P* values less than 0.05 were considered to be statistically significant.

3. Results

3.1. Patients with OSAHS versus those without OSAHS

Patients with OSAHS and those without OSAHS showed comparable data in area of S-fat, L/S ratio, serum AST and ALT, whereas the area of V-fat and V/S ratio in addition to serum levels of TG and FPG were significantly higher in patients with OSAHS (Table 1). These results confirmed the previous observation that OSAHS was associated with V-fat accumulation [4].