Obstructive sleep apnea syndrome (OSAS) is a very common disorder, and recent studies have suggested that OSAS affects up to 4 to 5% of the general population (1, 2) in the USA, Europe and Australia. OSAS is now being increasingly recognized in Japan. The rate of mortality is increased in untreated patients with OSAS, and patients with OSAS are also at an increased risk for cardiovascular disease (3, 4). Obese subjects are also more prone to develop OSAS (1). Although the body weight of OSAS patients does not change significantly after nasal continuous positive airway pressure (NCPAP) treatment (5), the rate of mortality due to cardiovascular diseases in OSAS patients is improved following NCPAP treatment (3). NCPAP treatment (6) can also improve repetitive obstructive sleep apnea with severe negative pressure, hypoxemia, microarousals and the associated changes in blood pressure and/or sympathetic nerve activity (7, 8). Therefore, obstructive sleep apnea with hypoxemia, microarousals and changes in blood pressure and/or sympathetic nerve activity might have an effect on the relationship between obesity and disease (Fig. 1). These phenomenon associated with OSAS may be viewed as stresses on patients with OSAS (Fig. 1). Heat shock proteins (HSPs), which are also called stress proteins, are a group of proteins induced in cells by various stresses; hyperthermia, osmotic stress, oxidative stress, ischemia, hypoxia, heavy metals, and amino acid analogs (9). HSP 72 is generally known to be a stress-inducible isoform that is barely detectable under unstressed conditions but which is rapidly synthesized during or after stress (9).

Extensive research on obesity has demonstrated that the location of the body fat deposits, rather than their size, is a more important determinant for the development of obesity-linked disorders. The accumulation of intra-abdominal visceral fat located in the mesenterium and omentum is a better predictor of leptin on insulin sensitivity in normal rats. Endocrinology 138: 3395–3401, 1997.


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Obesity and Sleep Apnea

Figure 1. Pathophysiology of obstructive sleep apnea syndrome.

of coronary heart disease than the body mass index (BMI) (10).

We investigated the blood coagulation system (11, 12), cardiac sympathetic nerve activity (13), expression of stress proteins (heat shock proteins) (14) and the location of body fat deposits in patients with OSAS before and after NCPAP treatment. These investigations (11–15) may enable us to understand the relationship between diseases and obesity, because the prevalence of patients with OSAS is so high (1, 2) and obese subjects are more prone to develop OSAS.

**OSAS and the coagulation system (11, 12)**

We measured the plasma fibrinogen concentration, which is an independent risk factor for cardiovascular events (16, 17), in the afternoon (3:30 PM) and the next morning upon awakening (8:30 AM) in 11 patients with OSAS (11 males, mean age 46±12.6 (SD) years, BMI 31.2±5.2 kg/m², apnea & hypopnea index (AHI) 62.9±20.9) before and after NCPAP therapy. In addition, Factor VII clotting activity (VIIc), which is also an independent risk factor for ischemic heart disease (18), was likewise investigated. The plasma fibrinogen and hematocrit levels in the morning were significantly higher than in the previous afternoon. The whole blood viscosity (WBV) at a shear rate of 208 inverse seconds (sec⁻¹), which can be predicted based on the hematocrit and total plasma protein (19), was also an independent risk factor for ischemic heart disease (18), was likewise investigated. The plasma fibrinogen and hematocrit levels in the morning were significantly higher than in the previous afternoon. The whole blood viscosity (WBV) at a shear rate of 208 inverse seconds (sec⁻¹), which can be predicted based on the hematocrit and total plasma protein (19), was also significantly higher in the morning. These increases in the plasma fibrinogen concentration and the WBV in the morning disappeared after NCPAP treatment (11), and the FVIIc levels gradually decreased following long-term NCPAP treatment (12). It has also been reported that the levels of platelet activation and aggregation were changed following NCPAP treatment (20).

**OSAS and cardiac sympathetic nerve function (13)**

To assess cardiac sympathetic nerve function in patients with OSAS, metaiodo-benzylguanidine (MIBG) cardiac scintigra-phy was performed in 11 OSAS patients (10 males and 1 female, age 43±16 years, BMI 31.3±5.2 kg/m², AHI 85.2±29.3). Cardiac sympathetic nerve function and integrity were found to be impaired in those subjects with OSAS when compared with age-matched controls. The mean value of the whole heart-to-mediastinum count ratios was closely correlated with the severity of the OSAS. Some of these impairments were significantly improved by NCPAP treatment.

**OSAS and stress proteins (14)**

Eleven OSAS patients (8 males and 3 females, age 50.2±16.4 years, BMI 33.7±5.7 kg/m², AHI 63.5±36.1) underwent polysomnography, and their peripheral blood mononuclear cells were isolated before, during and after sleep. The HSP72 protein levels were determined by Western blotting, and the hsp72 mRNA level was quantified by Northern blotting. The HSP72 levels decreased progressively during sleep, and the level at 8:00 AM was 78.0±17.5% of the value at 8:00 PM (p<0.01). No such decrease was seen in the normal subjects. When the OSAS patients received NCPAP therapy, the HSP72 levels did not decrease significantly. In untreated OSAS patients, the hsp72 mRNA levels decreased during sleep (p<0.01). When the patients were treated with NCPAP therapy, this decrease in the hsp72 mRNA levels was not observed except at 2:00 AM. The HSP72 protein levels before sleep in OSAS patients were significantly higher than in normal subjects (p<0.01). Repetitive apneas caused high HSP72 levels before sleep in OSAS patients, and therefore NCPAP therapy had a significant effect on the HSP72 levels during sleep.

**OSAS and visceral fat accumulation**

To determine the effects of NCPAP treatment on visceral fat accumulation (VFA) located in the intra-abdominal mesenterium and omentum, the amount of abdominal fat was assessed by a computerized tomographic (CT) method before
and after more than 6 months of NCPAP treatment. Long-term NCPAP treatment had a significant effect on the abdominal fat deposits.

Thus, OSAS has significant effects on the blood coagulation system, cardiac sympathetic nerve function, the levels of heat shock protein 72 expression, and lipid metabolism, which could in turn have a significant correlation with the morbidity of several diseases. Therefore, when obesity-linked disorders are investigated, it is important to consider the existence of OSAS in these obese patients because the prevalence of OSAS is so high (1, 2).


References


3. Role of Adipocytokines on the Pathogenesis of Atherosclerosis in Visceral Obesity

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Key words: visceral fat, adipocytokine, plasminogen activator inhibitor-1

Abstract

Obesity which is defined as accumulation of excess body fat, is a major cause of atherosclerotic vascular disease in industrial countries. Recent advances in the biology of adipose tissue have revealed that adipose tissue is not simply an energy storage organ but it also secretes a variety of molecules which...