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Review article

Obstructive sleep apnea syndrome is a systemic disease. Current evidence

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Abstract

Obstructive sleep apnea syndrome (OSAS) is a highly prevalent sleep disorder, characterized by repeated disruptions of breathing during sleep. This disease has many potential consequences including excessive daytime sleepiness, neurocognitive deterioration, endocrinologic and metabolic effects, and decreased quality of life. Metabolic syndrome is another highly prevalence emerging public health problem that represents a constellation of cardiovascular risk factors. Each single component of the cluster increases the cardiovascular risk, but the combination of factors is much more significant. It has been suggested that the presence of OSAS may increase the risk of developing some metabolic syndrome features. Moreover, OSAS patients are at an increased risk for vascular events, which represent the greatest morbidity and mortality of all associated complications.

Although the etiology of OSAS is uncertain, intense local and systemic inflammation is present. A variety of phenomena are implicated in this disease such as modifications in the autonomic nervous system, hypoxemia–reoxygenation cycles, inflammation, and coagulation–fibrinolysis imbalance. OSAS patients also present increased levels of certain biomarkers linked to endocrine-metabolic and cardiovascular alterations among other systemic consequences. All of this indicates that, more than a local abnormality, OSAS should be considered a systemic disease.

Keywords: Obstructive sleep apnea syndrome; Metabolic syndrome; Cardiovascular disease; Systemic disease; Continue positive airway pressure

1. Introduction

Obstructive sleep apnea syndrome (OSAS) is a common disorder. In a middle-aged population, Young et al. found that 2% of women and 4% of men presented this disorder [1]. The most common symptoms of OSAS patients include chronic loud snoring, excessive daytime sleepiness, personality changes and deterioration of quality of life. OSAS has been associated to an increased risk for automobile accidents [2,3] and for cardiovascular morbidity [4,5].

OSAS manifests as a reduction or complete cessation of airflow despite ongoing inspiratory efforts, as well as changes in nasal and oral airflow triggering hypoxemia and hypercapnia. The results may be arousal from sleep before resumption of breathing [6]. These abnormal respiratory events and arousals may occur many times throughout the night. The repetitive hypoxia and subsequent reoxygenation phenomena may cause oxidative stress and contribute to cardiovascular consequences [7,8]. In addition, OSAS has been found to be associated with obesity [9], inflammation [10] and metabolic dysregulation [11,12]. All of these indicate that, more than a local abnormality, OSAS should be considered a systemic disease. The systemic impact of OSAS mainly involves metabolic and cardiovascular consequences. The present review analyses the principal biomarkers related to the systemic consequences of OSAS.

2. OSAS and systemic inflammation

Although the etiology of OSAS is uncertain, intense local and systemic inflammation are present [13,14]. Several cytokines exhibit a high degree of temporal regulation as well as somnogenic potency such as interleukin-1 or TNFα [15]. The alteration or dysregulation of these cytokines may lead to sleep dysfunction.

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Several years ago, Entzian et al. showed that the circadian rhythm of TNFα release was significantly disturbed in OSAS patients; i.e. nocturnal physiologic peaks in this cytokine almost disappeared and an additional daytime peak developed [16]. More recently, it has been found that OSAS patients present increased levels of inflammatory mediators such as TNFα and IL-6 [17–21]. These abnormalities decrease with continue positive airway pressure (CPAP) treatment [10,22]. Based on these data and other clinical observations [23], it can be hypothesized that cytokines, mainly TNFα, play a role in the pathophysiology of OSAS. However, the fact that these alterations are also present in diseases such as narcolepsy has generated some controversy as the significance of these cytokines in OSAS. Indeed, it may be that they simply play a mediating role in diseases displaying excessive daytime sleepiness. Nevertheless, recent studies have shown that emergence of sleepiness in the context of OSAS does not appear to result from the selective increase of any particular somnogenic substance, such as TNFα or IL-6, in the context of sleep-disordered breathing [21].

Another interesting line of recent research in this field involves TNFα antagonists. A variety of studies have shown that sleepiness is affected by some medications that neutralize TNFα. These TNFα antagonists have rapidly emerged as a valuable class of antirheumatic agents. Examples include etanercept, a dimerized version of the soluble TNF receptor II, and infliximab, a chimeric anti-TNFα monoclonal antibody. Vgontzas et al. reported that obese OSAS patients presented significant and marked decrease in sleepiness after application of etanercept. This effect was reported to be much more effective than CPAP [24]. Zamarron et al. have shown that disturbances in sleep and alertness associated to rheumatoid arthritis improve with infliximab treatment. Improvement appears unrelated to joint discomfort amelioration, suggesting a central effect through inhibition of circulating TNFα [25].

3. OSAS and adiponectins

OSAS often coexists with obesity [26]. In fact, significant OSAS is present in approximately 40% of obese individuals, and about 70% of OSAS patients are obese [27].

In recent years, much attention has been focused on the interaction between OSAS and products released by adipose tissue such as leptin, adiponectin, resistin and ghrelin [28,29].

Leptin is an adipocyte-derived hormone that regulates body weight through control of appetite and energy expenditure [30]. Several studies have shown increased levels of leptin in OSAS and leptin resistance is likely to play a role in this disease [31–33].

The mechanisms underlying this relation are very diverse, and may involve the effects of overnight changes in apnea levels [34], sleep hypoxemia [35], and hypercapnia [36]. Previous work with animal obesity models has shown leptin to be related to ventilation control [37], as this hormone may represent a compensatory response to hypoventilation [38].

Obesity is a major confounding factor in the association between leptin and OSAS [39]. In a prospective study of 85 consecutive male patients referred for suspected OSAS, Schafer determined that the levels of leptin correlated with the levels of obesity biochemical markers [40].

Nevertheless, the direct relationship between OSAS and leptin is supported by the fact that effective OSAS treatment with CPAP also influences leptin levels [41]. Although the precise mechanism explaining the effect of CPAP has not yet been elucidated, it can be inferred that reduction in sympathetic activity [42] and improvement in insulin sensitivity play a role [43].

Adiponectin is an adipocyte-derived cytokine with regulatory functions in glucose and lipid metabolism. It also has profound anti-inflammatory and antiatherogenic effects. Levels of plasma adiponectin are decreased in obesity, and metabolic syndrome [44]. OSAS has independently been associated with reduced levels of adiponectin, which decrease as OSAS becomes more severe [45,46]. CPAP treatment of OSAS does not effectively normalize adiponectin levels [47] leading some authors to suggest that decreased adiponectin is the result of obesity [48]. Other possible causes include increased sympathetic activity [49], and higher levels of cytokines such as IL-6 and TNFα [50].

Resistin is a white adipose tissue hormone whose physiological function has yet to be established. In a study of 20 obese OSAS patients, Harsch et al. found a weak link between resistin and insulin sensitivity. CPAP treatment of OSAS had no significant influence on resistin levels [51].

Ghrelin is a hormone that influences appetite and fat accumulation and its physiological effects are opposite to those of leptin. No clear relation has been found between ghrelin and OSAS. In a study of 30 obese OSAS patients, Harsch found that plasma ghrelin levels were significantly higher in OSAS patients than in controls. The elevated ghrelin levels could not have been determined by obesity alone, since they rapidly decreased with CPAP therapy [52]. In a study of 30 untreated obese patients with moderate–severe OSAS, significantly higher levels of serum leptin were found in OSAS patients than in controls, but ghrelin levels presented no such difference [53]. Thus, the relation between OSAS and ghrelin is still an unresolved issue.

4. OSAS and endocrine-metabolic consequences

Even though OSAS is generally less prevalent in women than men, differences diminish after the onset of menopause. This may be the result of declining estrogen and progesterone [54,55]. Accordingly, estrogen replacement therapy in menopausal women lessens the prevalence of OSAS [56,57].

On the other hand, men diagnosed with OSAS may manifest decreased libido and a decline in morning serum testosterone levels [58,59]. At first, this was thought to reflect an associated dysfunction of the pituitary–gonadal axis related to sleep fragmentation and hypoxia [60]. However, the correction of hypoxia and sleep fragmentation