Obesity: the major preventable risk factor of obstructive sleep apnea

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An incre asing prevalence of obesity has led to an increase in the incidence of sleep disordered breathing in the general population. Obesity is associated with anatomic alterations that predispose to upper airway obstruction during sleep, leading to complete or partial cessation of respiration called obstructive sleep apnea. The awareness of this global issue is rising, and health care systems are providing preventive measures, diagnostic, and treatment options for both conditions. To decrease obesity, lifestyle modification (eating behaviors, smoking, drinking alcohol, etc.) and understanding the importance of exercise are needed. If these lifestyle modifications are widely applied, then not only obesity and sleep apnea will be reduced but also the incidence of serious consequences such as cardiovascular disease and health care costs will decrease greatly.

Keywords:
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Introduction

Obstructive sleep apnea (OSA) syndrome is common, with a prevalence of ~2–4% in middle-aged men and women [1]. Frequent partial (hypopnea) or complete (apnea) closure of the upper airway during sleep leads to oxygen desaturation, increased respiratory effort, arousal, and sleep fragmentation. Patients typically present with witnessed apneas, loud intermittent snoring, and excessive daytime somnolence [2]. The syndromes are associated with impairment in quality of life [3], cognitive function, work performance [4], and with an increased risk of road-traffic accidents [5]. OSA is considered an independent risk factor for hypertension [6,7] and has associations with coronary artery disease [8], stroke [9], heart failure [10], arrhythmias [11], metabolic syndrome [12], and type 2 diabetes [13].

Obesity is an important risk factor for the development of OSA [14–16] and is unique among the major risk factors in being preventable and modifiable [17]. Many studies evaluated the effects of weight loss, achieved by behavioral, pharmacological, and surgical approaches, in the management of OSA in the obese patients.

Obesity as a risk factor for obstructive sleep apnea

The role of excess weight as a causal factor of OSA has been confirmed by many studies. The prevalence of OSA in obese or severely obese patients is nearly twice that of normal-weight adults [17]. In a population study involving 2148, the prevalence of obesity was significantly higher in those with OSA than those without, whether male (22 vs. 8%) or female (32 vs. 18%) [18]. Another study of 161 obese patients (BMI ≥30 kg/m^2) showed that OSA was present in more than 50%, and in 25%, this was severe [19]. Among the morbidly obese patients (BMI ≥40 kg/m^2), the prevalence of OSA as high as 98% has been reported [20].

Using data from the population-based Wisconsin Sleep Cohort Study [1], Young *et al.* [16] estimated that, in 41% of adults with mild or worse sleep disordered breathing (SDB) [apnea hypopnea index (AHI) ≥5) and in 58% of those with moderate or worse SDB (AHI ≥15), SDB was attributable to excess weight (defined as BMI ≥25 kg/m^2). In a study based on data from the 2005 National Sleep Foundation Sleep in America poll, 59% of 379 obese individuals were at high risk for OSA as defined by the Berlin Questionnaire [21].

In the Sleep Heart Health Study based on 5615 adults, the odds ratio for an AHI of 15 or greater with a BMI difference of 10 kg/m^2 was 2.4 [22]. A longitudinal population-based study demonstrated that a 10% weight gain predicted a 32% increase in AHI whereas a 10% weight loss predicted a 26% decrease in AHI. Furthermore, a 10% increase in weight predicted a six-fold increased

risk of developing moderate-to-severe SDB [23]. This association was stronger for males than for females [24].

Likewise, other relevant anthropometric measures have been associated with OSA such as neck circumference [22,25–27], waist circumference [28], waist-hip-ratio [29], and visceral adiposity [30,31].

Mechanisms for the development of obstructive sleep apnea in the obese patients

There are several mechanisms by which obesity could result in OSA, and these may act synergistically. It is proposed that increased peri-pharyngeal fat deposition results in mechanical loading that offsets the maintenance of airway patency by the dilator muscles and that this increase in collapsibility is particularly prominent during sleep when there is a reduction in neuromuscular activity [32–34]. In addition, there is some evidence to suggest that central obesity in particular may have detrimental effects on neuromuscular activity in the upper airway [35].

Obesity also is associated with a reduction in functional residual capacity (FRC) [36]. Pharyngeal collapsibility may be further accentuated by this reduction in FRC with subsequent decrease in tracheal traction on the pharynx [34].

Finally, a self-perpetuating cycle may develop in which sleep disruption leads to increased appetite (especially for calorie-rich high-carbohydrate foods) [37], reduced activity levels, further weight gain, and increased severity of OSA [38].

Adipokine modulators in obesity and obstructive sleep apnea

Obesity and sleep apnea are often associated with dysregulation of glucose and lipid metabolism [39–42], although the precise mechanisms for these associations are not well understood.

As fat accumulates in adipose stores, it secretes humoral factors or adipokines that may influence upper airway function during sleep. On the one hand, these factors regulate the distribution of body fat between the central (visceral) and peripheral (subcutaneous) compartments, which can influence mechanical loads on the upper airway [43,44].

In humans, leptin rises with increasing obesity and is secreted preferentially by subcutaneous rather than visceral fat [45,46], thus accounting for higher serum concentrations in women than men [47].

In contrast, adiponectin rises steeply with weight loss [48], and especially with the loss of visceral adiposity [49,50]. Thus, leptin and adiponectin may lower sleep apnea susceptibility by reducing central adiposity and pharyngeal structural loads.

In addition, adipose tissue elaborates humoral factors that may act centrally on the regulation of upper airway neuromuscular control. Leptin has been demonstrated to stimulate CO_2 ventilatory responses in mice [43,51–53]. Its action is antagonized by other adipose-related factors, namely, the soluble leptin receptor and C-reactive protein [54], which bind circulating leptin and can decrease its central nervous system uptake and action [54,55]. Levels of soluble leptin receptor and C-reactive protein are elevated in sleep apnea compared with matched control patients [56,57] and decline with weight loss and the loss of visceral compared with central adiposity.

Other adipokines, including tumor necrosis of factor-alpha, interleukin-1b, and interleukin-6, are markedly elevated in obesity and especially in central obesity [45,46,56]. Their somnogenic activity may lead to a global depression on central nervous system activity and upper airway neuromuscular control [58–61]. As disturbances in upper airway neuromotor control ensue, increases in sleep apnea severity [62] can trigger further elevations in proinflammatory cytokines and exacerbate sleep apnea [56,57,63–68].

Obesity and obstructive sleep apnea in children

The higher prevalence of OSA in obese patients is not limited to adults; recent data show that obese children have a 46% prevalence of OSA when compared with children seen in a general pediatric clinic (33%) [69]. This finding is further aggravated by the obesity epidemic among children and adolescents [70]. In fact, there are data suggesting that children and adolescents with OSA have more than a six-fold increased risk of having metabolic syndrome, when compared with children and adolescents without OSA [71].

These findings highlight the need to develop screening and prevention measures for these conditions, even as early as in childhood. It is possible that obesity may worsen OSA because of fat deposition at specific sites. Fat deposition in the tissues surrounding the upper airway appears to result in a smaller lumen and increased collapsibility of the upper airway, predisposing to apnea [33,72]. Moreover, fat deposits around the thorax (truncal obesity) reduce chest compliance and FRC, and may increase oxygen demand [73].

Genetic link of obesity and obstructive sleep apnea

There are data showing substantial overlap in genetic substrates between OSA and obesity. Patel *et al*. [74] reported a significant correlation between AHI and anthropomorphic adiposity measures (range, 0.57–0.61), suggesting that obesity could explain nearly 40% of the genetic variance in sleep apnea.

In another study, Popko *et al*. [75] showed that polymorphisms (Arg–Arg and Gln–Arg when compared with Gln–Gln) of the leptin receptor, which is involved in energy homeostasis and body weight regulation, are significantly correlated with both OSA and obesity when compared with healthy controls. These studies suggest that genetic polymorphisms may influence both sleep apnea and obesity and may be importantly interrelated in the development of these conditions.

Treatment implications of obesity in obstructive sleep apnea

Weight loss remains a highly effective strategy for treating sleep apnea [76,77]. It can be achieved with exercise, diet changes, and/or medications. In two controlled studies, investigators have demonstrated that a 10–15% reduction in body weight leads to an ~50% reduction in sleep apnea severity (AHI) in moderately obese male patients [76,77].

In recent years, bariatric surgical procedures have been increasingly used for the treatment of severe obesity. These procedures combine gastric restriction and/or intestinal bypass to induce early satiety and nutrient malabsorption, respectively [78–82], and lead to an ~60% loss in excess body weight in the first 12–18 months postoperatively [83,84]. In a recent meta-analysis of bariatric studies involving 22 094 patients, Buchwald *et al*. [85] have documented dramatic improvement in the vast majority of patients after surgery, with reductions in AHI of 33.9 episodes/h and sleep apnea resolution in 85.7% of patients.

Improvements in sleep apnea with weight loss have been related to effects of adiposity on upper airway function during sleep. In controlled weight loss intervention studies, we demonstrated decreases in upper airway collapsibility during sleep with weight loss. This was attributed to reductions in mechanical loads or improvements in pharyngeal neuromuscular control [76,77]. These mechanisms may be related to alterations in humoral factors, including ghrelin, adiponectin, and leptin, which have been linked to changes in body weight and regional adiposity and account for wide variations in sleep apnea and upper airway responses to weight loss [86,87].

Conclusion

Obesity is a major risk factor for OSA. The prevalence of OSA is increased in the obese patients and vice versa and the severity of OSA increases in association with weight increase. Pathophysiological mechanisms by which obesity can lead to OSA have been identified. Weight loss may lead to an improvement in the severity of OSA and perhaps even its resolution.

To be successful, weight loss has to be maintained in the long term to prevent relapse, and 'weight loss programs' are mandatory in this group of population. The success of such programs is usually affected by the motivation of the individual and his support group.

This review highlights the effect of obesity on OSA. This implies public health awareness that demands multicentered interventions. Moreover, making dietary changes and engaging in physical exercise should be encouraged. If medical and/or lifestyle medication therapies fail, then surgical interventions are another option to treat obesity and its associated comorbidities in obese patients with OSA.

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Conflicts of interest

There are no conflicts of interest.

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