Abdominal Fat and Sleep Apnea

The chicken or the egg?

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Obstructive sleep apnea (OSA) syndrome is a disorder characterized by repetitive episodes of upper airway obstruction that occur during sleep. Associated features include loud snoring, fragmented sleep, repetitive hypoxemia/hypercapnia, daytime sleepiness, and cardiovascular complications. The prevalence of OSA is 2–3% and 4–5% in middle-aged women and men, respectively. The prevalence of OSA among obese patients exceeds 30%, reaching as high as 50–98% in the morbidly obese population. Obesity is probably the most important risk factor for the development of OSA. Some 60–90% of adults with OSA are overweight, and the relative risk of OSA in obesity (BMI >29 kg/m^2) is ≥10. Numerous studies have shown the development or worsening of OSA with increasing weight, as opposed to substantial improvement with weight reduction. There are several mechanisms responsible for the increased risk of OSA with obesity. These include reduced pharyngeal lumen size due to fatty tissue within the airway or in its lateral walls, decreased upper airway muscle protective force due to fatty deposits in the muscle, and reduced upper airway size secondary to mass effect of the large abdomen on the chest wall and tracheal traction. These mechanisms emphasize the great importance of fat accumulated in the abdomen and neck regions compared with the peripheral one. It is the abdomen much more than the thighs that affect the upper airway size and function. Hence, obesity is associated with increased upper airway collapsibility (even in nonapneic subjects), with dramatic improvement after weight reduction. Conversely, OSA may itself predispose individuals to worsening obesity because of sleep deprivation, daytime somnolence, and disrupted metabolism. OSA is associated with increased sympathetic activation, sleep fragmentation, ineffective sleep, and insulin resistance, potentially leading to diabetes and aggravation of obesity. Furthermore, OSA may be associated with changes in leptin, ghrelin, and orexin levels; increased appetite and caloric intake; and again exacerbating obesity. Thus, it appears that obesity and OSA form a vicious cycle where each results in worsening of the other.

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Although interest in sleep and dreams has existed since the dawn of history, it has only been in the last 25–35 years that physicians have recognized the importance of sleep disorders, and only in the last 20–25 years that sleep laboratory services have been commonly available. Over the recent years, several categories of sleep disorders were recognized, with special interest in breathing disorders during sleep. It is quite clear now that quantity and quality of life deteriorates secondary to sleep disordered breathing, with complex associations between sleep-disordered breathing and obesity, cardiac diseases, stroke, and diabetes.

Obstructive sleep apnea (OSA) syndrome is characterized by the recurrent collapse of the pharyngeal airway during sleep, which generally requires arousal to reestablish airway patency and resume breathing. Thus, the patient suffers from both sleep fragmentation (frequent arousal) and the recurrent hypoxemia and hypercapnia resulting from the respiratory pause. As a result, the potential adverse consequences can be decreased neurocognitive function (sleepiness, mood changes), cardiovascular complications (systemic and pulmonary hypertension, cor pulmonale, arrhythmias, myocardial infarction, and stroke), and ultimately death. Associated features include loud snoring, dry mouth upon awakening, morning headaches, heartburn, nocturia, daytime sleepiness, and sexual dysfunction in men. The diagnosis is typically confirmed by overnight polysomnography, during which sleep is recorded while breathing, and respiratory effort, oxygen saturation, and electrocardiogram are simultaneously monitored. Ambulatory studies emerge and the diagnosis is sometimes made during a home sleep study. Upper airway obstruction can be complete, in which case there is no airflow (obstructive apnea) or partial, during which there is a substantial reduction in, but not a complete cessation of, airflow (obstructive hypopnea). Patients with sleep apnea are typically characterized by an apnea-hypopnea index or respiratory disturbance index, which is the average number of apneas plus hypopneas per hour of sleep. The magnitude of the oxygen desaturations is an additional measure commonly used to indicate the severity of the disorder. Generally in adults, respiratory disturbance index <5 is considered normal. The mild apnea range includes a respiratory disturbance index <20 and minimal oxygen saturation not lower than 85%, whereas the severe range includes respiratory disturbance index >40 or minimal oxygen saturation <65%. The range in between is considered of moderate severity.

The most important risk factor for OSA is obesity in general and central obesity in particular. While it is well documented that obesity can result in OSA via several mechanisms, recent evidence suggests that OSA can worsen obesity. Thus, it appears that there are complex associations between OSA and obesity.

EPIDEMIOLOGICAL ASPECTS

— The prevalence of OSA syndrome may somewhat change based on the definition used. The most commonly used definition of OSA is the combination of respiratory disturbance

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Abbreviations: CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

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index of over five events per hour of sleep plus a complaint of daytime somnolence. When these definitions were used in a large-scale population-based study, the reported prevalence was 2 and 4% in middle-aged women and men, respectively (1). Using the same definitions in a recent Korean study, the prevalence of OSA was found to be 4.5% in men and 3.2% in women (2). Several other ethnicity-specific epidemiological studies revealed that the prevalence of OSA is similar or somewhat higher in Asian, Indian, Hispanic, and Afro-American populations than in Caucasian populations (3–6). It is unclear, however, at this time whether the increased prevalence in some specific ethnic group results from direct genetic causes or from ethnic-related characteristics of body phenotype such as upper airway structure or obesity (6). Recently, several community-based studies have been performed to learn more about the prevalence and impact of sleep-disordered breathing on general health. In the Sleep Heart Health Study, it was reported that >10% of the general population has some degree of sleep-disordered breathing, with daytime somnolence correlated to the breathing disorder severity (7). Furthermore, in a report of over 15,000 individuals from the Sleep Heart Health Study, it has been estimated that although the prevalence of OSA is over 4%, only 1.6% had such a diagnosis by their physician, and only 0.6% were actually treated for OSA, indicating under-diagnosis and under-recognition of this important disorder (8). Because OSA is linked to several risk factors and associated diseases, several epidemiological studies reported on increased prevalence of OSA in patients with hypothyroidism (9), diabetes (10,11), gastro-esophageal reflux (12), and others (13–17). In populations with cardiovascular diseases, the prevalence has been found to be substantially increased, especially in patients with hypertension (18–20). The prevalence has been also reported to be increased in patients with stroke (21), renal failure (22,23), and heart failure (24). Of special concern is the high prevalence of OSA reported in professional drivers (25) because of the known increased risk of traffic accidents. Thus, obstructive sleep apnea is a common disorder both in the general population and even more in specific populations at risk, the most impressive of which is obesity.

The prevalence of OSA among obese patients has been reported to exceed 30% (26,27), reaching as high as 50–98% in the morbidly obese population (28,29). Some 60–90% of adults with OSA are overweight, and the relative risk of sleep apnea from obesity (BMI >29 kg/m^2) may be as great as 10 or more (27,30–35). Furthermore, it has clearly been shown that OSA worsens with weight gain and improves with weight reduction (34,36–41). Obesity was reported to be the most important demographic predictor of sleep-disordered breathing in a population-based survey (42). Furthermore, OSA correlated best with neck size (which increases with central obesity) even more than with general obesity, in a population-based study of over 1,000 men (43). Thus, epidemiologically the association between obesity and OSA is well documented. Mechanistically, several obesity-related effects have been suggested.

PATHOPHYSIOLOGY — The principle abnormality in obstructive sleep apnea is an anatomically small pharyngeal airway. During wakefulness, the individual is able to compensate for the deficient anatomy, by increasing the activity of upper airway muscles that maintain airway patency. However, with sleep onset, this compensation is lost and airway collapse occurs. The physiological consequences of apnea are a rise in $PaCO_2$, a fall in PaO_2, and increasing ventilatory effort against an occluded airway. Ultimately, transient arousal from sleep occurs, which reestablishes the airway and ventilation. The individual subsequently returns to sleep and the cycle begins again, to be repeated frequently over the course of the night (44).

PHARYNGEAL ANATOMY — Several studies, using a variety of imaging techniques (computed tomography, magnetic resonance imaging, acoustic reflection, and cephalometrics) have demonstrated a small pharyngeal airway in patients with OSA (45–54). Smaller airway size may result from several syndromes or anatomical and skeletal structures, but always worsens with increasing body fat and obesity (55–57). When luminal size is narrower, it makes the airway vulnerable to collapse (44). On top of direct fat deposits within the airway luminal walls, upper airway size may be smaller in obese patients because of reduced lung volume (functional residual capacity) (58). It has been shown that in obese patients with OSA, pharyngeal cross-sectional area is abnormally small and varies considerably with changes in lung volume. Pharyngeal area decreased significantly over the vital capacity range from total lung capacity to residual volume (58), probably because of reduced tracheal traction. Both inspiratory increases and tonic thoracic traction (pull of the thorax) on the trachea, characteristic of lean versus overweight individuals, have been shown to improve patency of the upper airway (59,60).

In addition to airway size, airway shape may also be an important determinant of upper airway collapsibility in general and in obesity in particular. While normally the antero-posterior/lateral luminal airway dimension is low, patients with OSA demonstrate an oval shape of the pharyngeal airway (i.e., a relatively high airway pressure/lateral luminal airway dimension) (61,62). When airway is oval in shape, there is a reduced ability of muscles to dilate the pharynx (63). In addition, the soft tissues surrounding the upper airway may have an independent role. Using sophisticated analyses of soft tissue variables, sleep apnea patients were shown to have increased thickness of the lateral pharyngeal walls, independent of fat pad thickness (at the level of the minimum axial airway lumen) (45,46,50,51–57). This finding is helpful in explaining the reduced lateral diameter of the airway lumen in apneics compared with non–weight-matched control subjects. No important skeletal differences were observed, implicating soft tissues as the major anatomic difference between apneics and control subjects. Schwab et al. (50,51) argued that lateral wall thickening and ultimately collapse are important components in the pathogenesis of OSA in adults. Thus, anatomical effects predisposing obese individuals for airway collapse include smaller airway cross-sectional area (reduced lumen size due to fatty tissue within the airway or in its lateral walls, reduced upper airway size secondary to mass effect of the large abdomen on the chest wall and trachel traction) and changing its shape into oval. These mechanisms emphasize the great importance of fat accumulated in the abdomen and neck regions compared with the peripheral region, since it is the abdomen much more than the thies, and the direct fat deposit in the

Table 1—*A brief summary of most studies investigating the association of OSA with various hormones and the effects of treatment with CPAP*

	Effect on appetite	Level in OSA	Effect of CPAP
Insulin	Decrease	Increased (insulin resistance)	Decrease
Leptin	Decrease	Increased (leptin resistance)	Decrease
Ghrelin	Increase	Increased	Decrease
Orexin	Increase	Conflicting results	Increase

pharyngeal area, that affect the upper airway size (31,32–64).

ROLE OF PHARYNGEAL MUSCLES

— The inspiratory dilator phasic upper airway muscles are activated during inspiration and counteract the collapsing influence of negative airway pressure. The genioglossus is the best studied such muscle. The activity of the genioglossus is substantially reduced during expiration when pressure inside the airway becomes positive and there are fewer tendencies for collapse. Other muscles such as the tensor palatini do not consistently demonstrate inspiratory phasic activity but instead maintain a relatively constant level of activity throughout the respiratory cycle. These are called tonic, or postural muscles, and are also thought to play a role in the maintenance of airway patency. Negative pressure in the pharynx (which would tend to collapse the airway) markedly activates these muscles, which in turn counteracts this collapsing influence (65–69). In patients with sleep apnea having anatomically small airways, a negative pressure reflex is substantially activated during wakefulness, leading to augmented dilator muscle activity as a neuromuscular compensatory mechanism to protect the airways (70). Therefore, the individual's propensity for upper airway collapse during sleep depends on two variables: *1*) the patient's predisposing anatomy and *2*) the level of pharyngeal dilator muscle activity.

The effect of sleep on upper airway muscle activity probably plays an important role in the pathophysiology of OSA. The protective reflex activation of these muscles that can be observed during wakefulness is markedly diminished during sleep. This reflex-driven augmentation of dilator muscle activity compensates for deficient anatomy in apnea patients during wakefulness. During sleep, there is a marked attenuation or loss of this reflex mechanism, even in normal subjects. Thus, the loss of the negative pressure reflex protecting mechanism with the reduced dependency of dilator muscle activation in negative pressure and rising CO_2 lead to falling dilator muscle activity and airway collapse (67,68,71,72).

The effect of obesity on upper airway dilator protecting muscle activation probably plays a substantial role in the tendency of obese individuals toward airway collapse. Several studies reported decreased upper airway muscle protective force or altered muscle structure due to fatty deposits within the muscle (46,73,74). This may result in increased collapsible velopharynx during wakefulness in obese individuals, which may predispose to upper airway obstruction during sleep. Indeed, it has been clearly shown that obesity is associated with increased upper airway collapsibility, with dramatic improvement after weight reduction (41,75). Velopharygeal compliance was found to be strongly correlated with neck circumference and BMI (74).

Thus, that obesity can result in upper airway collapsibility and vulnerability to OSA is well established. The major causes are briefly presented in Fig. 1 (*right side*). However, recent evidence suggests that OSA can also predispose individuals to gain weight. These mechanisms are displayed on the *left side* of Fig. 1 and are discussed below.

BEHAVIORAL CONSEQUENCES

— Numerous studies have pointed out the reduced sleep efficiency and non-refreshing nature of sleep in patients with sleep apnea. Sleep is fragmented, with reduced slow-wave sleep and REM sleep, and one of the most prominent symptoms of OSA is excessive daytime somnolence (76–81). Although not strongly correlated, increasing severity of OSA results in both subjective and objective sleepiness, which can consequently result in increased prevalence of occupational and traffic accidents (82–87). Daytime sleepiness may result in decreased mood and decreased physical activity, which if not associated with reduced caloric intake, will obviously worsen obesity. Indeed, it has been shown that obesity and OSA are associated with reduced physical activity, which increases after weight reduction surgery (88). Thus, theoretically patients with OSA are at high risk of gaining weight and subsequently worsening their OSA. When treated, patients manage to improve alertness and daytime activity (80,89). If remained untreated, some patients tend to gain weight and the apnea becomes worse (34,90). The metabolic balance of sleep apnea and obesity seems to result from a complex balance between several regulatory hormones.

HORMONAL CHANGES

— It is well established that sleep deprivation de-

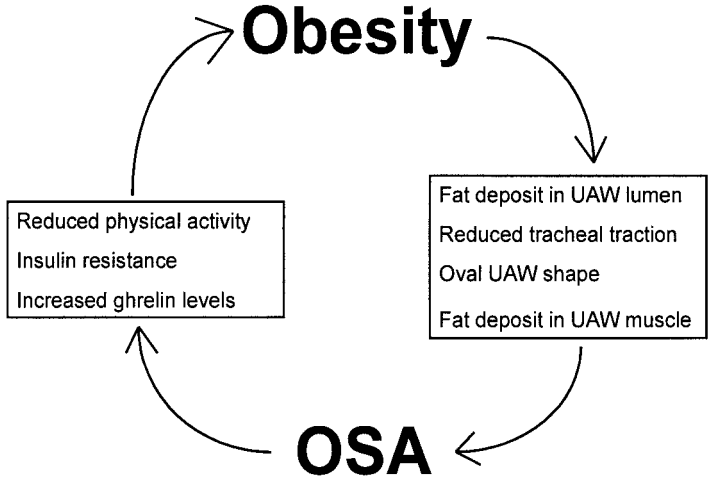

Figure 1—*Potential mechanisms formatting a vicious cycle where obesity may result in OSA and OSA may lead to weight gain (see text for details). UAW, upper airway.*

creases glucose tolerance and results in insulin resistance (91–93). A growing body of epidemiological evidence supports an association between chronic partial sleep deprivation (short sleep duration) and the risk for obesity, insulin resistance, and diabetes (94). Sleep deprivation for 24 h decreased the insulin sensitivity in healthy subjects without changes in cortisol levels (91). It was suggested that sleep deprivation results in decreased insulin sensitivity at peripheral receptor sites, which can eventually lead to insulin exhaustion at pancreatic sites, after longer periods of sleep deprivation (92). Because OSA is associated with sleep fragmentation, effectively sleep loss and daytime sleepiness, the insulin sensitivity in patients has been assessed and indeed insulin resistance has been reported (95–97). That OSA is an independent risk factor for increased insulin resistance can be learned from improvement in insulin sensitivity after 3 months (but not 2 days) of treatment with continuous positive airway pressure (CPAP) (98). However, the exact mechanism leading to insulin resistance in patients with OSA is not fully understood. One option is the effective sleep deprivation associated with OSA, and an additional potential mechanism may involve the elevated sympathetic activity in OSA (98). In a later and larger scale study by the same group, the authors reported that insulin sensitivity significantly increased after 2 days and remained stable after 3 months of CPAP treatment. The improvement in insulin sensitivity in the short-term treatment (2 days) was more marked in less obese patients. The authors suggested that in obese individuals, insulin sensitivity is mainly determined by obesity (as they were less affected by CPAP) and to a lesser extent by OSA (99). To learn about the mechanism of insulin resistance in OSA, Polotsky et al. (100) studied a model of intermittent hypoxia in lean and obese-leptin–deficient mice. In lean mice, intermittent hypoxia resulted in a decrease in fasting blood glucose levels, improvement in glucose tolerance without a change in serum insulin levels, and an increase in serum leptin levels in comparison with control. Leptin was the only upregulated gene affecting glucose uptake. In obese mice, short-term intermittent hypoxia led to a decrease in blood glucose levels accompanied by an increase in serum insulin levels, which was abolished by prior leptin infusion. Obese mice exposed to intermittent hypoxia for 12 weeks (long term) developed a time-dependent increase in fasting serum insulin levels and worsening glucose tolerance, indicating insulin resistance. The authors concluded that the increase in insulin resistance in response to prolonged intermittent hypoxia was dependent on the disruption of leptin pathways (100). In a recent study of humans with OSA, Babu et al. (101) reported that 83 days on CPAP resulted in significant reduction of glucose levels as well as A1C, with a significant correlation between CPAP treatment and reduction in A1C.

Leptin is a protein produced by adipose tissue that circulates to the brain and interacts with receptors in the hypothalamus to inhibit eating and control of body weight and fat distribution (Table 1). There is growing evidence that leptin regulation is altered in OSAS. Most studies reported on increased leptin levels in patients with OSA (95,102–104), which were commonly correlated with an apnea-hypopnea index (95,102). Furthermore, specific treatment of OSA with nasal CPAP resulted in decrease in leptin levels (95,105,106). It was suggested that hyperleptinemia may be a prognostic marker of OSA (102). Because leptin levels are high in patients with OSA independent of body fat content, it was postulated that OSA is associated with resistance to the weight-reducing effects of leptin (103), which may in turn result in increased appetite and weight gain.

Another relatively recently discovered hormone that regulates appetite and body weight is ghrelin. In a recent study of patients with OSA and BMI-matched control subjects, ghrelin levels were shown to be significantly higher in patients with OSA (107). CPAP treatment of 2 days was sufficient to significantly reduce ghrelin levels in these patients (107). The appetite stimulating effects of ghrelin may well contribute to increased caloric intake and weight gain in patients with OSA.

Orexin (also called hypocretin) is also an additional appetite-stimulating neuropeptide. Hypocretin-1 and -2, or orexin-A and -B, are produced by lateral hypothalamic neurons and participate in the control of feeding, sleep, wakefulness, neuroendocrine homeostasis, and autonomic regulation. Initially, a role in appetite control was suggested as the main action of the two hypothalamic neuropeptides, since their site of synthesis and incretion, the lateral hypothalamus, is primarily involved in the control of food ingestion. Destruction of lateral hypothalamic areas results in underfeeding, and orexins were thought to be the substances mediating appetite-stimulating drives. However, further studies indicate a more complex array of functions and effects (108). While orexin levels are clearly important for vigilance and are low (undetectable) in somnolence disorders such as narcolepsy, in OSA, there are inconsistent reports. Studies reported both increased levels (109) and reduced levels (110) of orexin in OSA. One study reported a positive correlation between an apnea-hypopnea index and orexin levels (109), which may potentially explain the tendency toward weight gain in patients with OSA. We have measured orexin in extremely sleepy patients after surgical removal of a craniopharyngioma tumor. Although we expected to find low levels, which would explain the severe sleepiness, we found normal and even high levels, which would explain the constant increase in body weight we observed in our patients (111).

In summary, it appears that there are complex relationships between obesity and OSA, with many factors affecting both. It is well established that obesity can result or worsen OSA, via several potential mechanisms. Whether OSA worsens obesity is less clear at this time, although there are several potential mechanisms that support such a sequence. Large-scale well-controlled studies may shed light on this complex subject.

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