

Obesity and Obstructive Sleep Apnea

Pathogenic Mechanisms and Therapeutic Approaches

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Obstructive sleep apnea is a common disorder whose prevalence is linked to an epidemic of obesity in Western society. Sleep apnea is due to recurrent episodes of upper airway obstruction during sleep that are caused by elevations in upper airway collapsibility during sleep. Collapsibility can be increased by underlying anatomic alterations and/or disturbances in upper airway neuromuscular control, both of which play key roles in the pathogenesis of obstructive sleep apnea. Obesity and particularly central adiposity are potent risk factors for sleep apnea. They can increase pharyngeal collapsibility through mechanical effects on pharyngeal soft tissues and lung volume, and through central nervous system-acting signaling proteins (adipokines) that may affect airway neuromuscular control. Specific molecular signaling pathways encode differences in the distribution and metabolic activity of adipose tissue. These differences can produce alterations in the mechanical and neural control of upper airway collapsibility, which determine sleep apnea susceptibility. Although weight loss reduces upper airway collapsibility during sleep, it is not known whether its effects are mediated primarily by improvement in upper airway mechanical properties or neuromuscular control. A variety of behavioral, pharmacologic, and surgical approaches to weight loss may be of benefit to patients with sleep apnea, through distinct effects on the mass and activity of regional adipose stores. Examining responses to specific weight loss strategies will provide critical insight into mechanisms linking obesity and sleep apnea, and will help to elucidate the humoral and molecular predictors of weight loss responses.

Keywords: sleep apnea; obesity; upper airway; pharynx; weight loss

Obstructive sleep apnea is a common chronic disease in Western society whose prevalence is estimated at 2% of women and 4% of men in the general population (1). It is characterized primarily by recurrent occlusion of the upper airway that results in oxyhemoglobin desaturation and periodic arousals from sleep (2). It now appears that even mild to moderate sleep apnea is associated with the development of hypertension, diabetes mellitus (3), and cardiovascular risk (4, 5). With increasing obesity, sleep apnea can contribute to the development of daytime alveolar hypoventilation (obesity hypoventilation syndrome), cor pulmonale, and frank respiratory failure (6, 7). Thus, given its high prevalence and morbidity, sleep apnea poses a significant clinical burden to Western society.

Concerns about the health impact of sleep apnea have been increasing in light of the growing epidemic of obesity in Western society and worldwide (8, 9). The most recent National

Health and Nutrition Examination Survey (NHANES) data document a dramatic rise in the prevalence of obesity, with prevalence estimates of approximately 60% (body mass index [BMI] > 25 kg/m³) and 30% (BMI > 30 kg/m³) in overweight and obese adults, respectively (10). The NHANES data also demonstrate that the prevalence of severe obesity (BMI > 40 kg/m²) has risen to epidemic proportions from 2.9% of the U.S. adult population in 1988–1994 to 4.8% in 2003–2004. Current data from the Behavioral Risk Factor Surveillance System indicate that increases in severe obesity have disproportionately affected African Americans, women, young adults, and those of lower socioeconomic status in American society (8, 9), and clinical data from bariatric case series document the presence of sleep apnea in the vast majority of the severely obese (11). Nevertheless, the mechanisms linking obesity to the development and progression of sleep apnea remain unclear.

SLEEP APNEA RISK FACTORS: ROLES OF OBESITY, SEX, FAT DISTRIBUTION, AND HERITABLE FACTORS

Several risk factors, including obesity, male sex, age, and heritable factors, have been associated with an increased prevalence of obstructive sleep apnea in the general population (1). Among these, obesity is one of the strongest sleep apnea risk factors (12–15). Mild to moderate obesity has been associated with markedly increased sleep apnea prevalence (3, 14, 16). In a community-based cohort of middle-aged subjects, Young and colleagues (1) showed that a 1-SD increase in BMI was associated with a fourfold increased risk for prevalent sleep apnea, and we have demonstrated a sleep apnea prevalence of approximately 40% in moderately overweight men from the community who are otherwise healthy (3). In severe obesity (BMI > 40 kg/m²), the prevalence of sleep apnea was estimated to vary between 40 and 90% (17–24), and the severity of sleep apnea was generally greater than that found in leaner clinical populations (17, 25, 26). In addition, Peppard and colleagues have provided further evidence for a link between sleep apnea and obesity by demonstrating that a 10% change in body weight was associated with a parallel change of approximately 30% in the apnea-hypopnea index (AHI), the major index of sleep apnea severity (16).

It is well recognized that male sex also constitutes a particularly strong risk factor and confers a two- to threefold increased risk of sleep apnea in the population at large (14, 27). This increased risk may be related to the differences in the distribution of adipose tissue in men (28–30), who exhibit a predominantly central fat deposition pattern around the neck, trunk, and abdominal viscera compared with women (31, 32). Increases in visceral fat with age may also account for an increase in sleep apnea prevalence in middle-aged and older men and in postmenopausal women (33). Newman and coauthors (34) have compared the effect of weight change on sleep apnea progression in male and female participants in the Sleep Heart Health Study, a multicentered epidemiologic cohort study of cardiovascular correlates of sleep apnea in middle-aged and older Americans. These authors demonstrated that

(Received in original form August 23, 2007; accepted in final form September 21, 2007)

Supported by National Institutes of Health grants HL50381 (principal investigator, A.R.S.) and HL37379 (principal investigator, P.L.S.), and M01RR02719 (Johns Hopkins Bayview General Clinical Research Center; principal investigator, Daniel Ford).

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Proc Am Thorac Soc Vol 5, pp 185–192, 2008

DOI: 10.1513/pats.200708-137MG

Internet address: www.atsjournals.org

relatively small increases in body weight were associated with an increasing severity of sleep apnea, and that this increase was particularly striking in men compared with women. Thus, obesity and central obesity constitute potent risk factors for the presence and progression of sleep apnea.

Despite the preponderance of evidence linking obesity and central adiposity with sleep apnea, considerable variability exists in the prevalence and severity of this disorder, even among those who are markedly obese. In severely obese patients presenting for bariatric surgery, sleep apnea severity did not correlate with the degree of obesity, as assessed by BMI (35). To determine the prevalence and severity of sleep apnea in markedly obese men and women, a large cohort of bariatric surgery patients ($n = 114$) was screened at the Johns Hopkins Sleep Disorders Center with overnight sleep studies. Using specific cutoff values of the AHI to define the prevalence and severity of sleep apnea, we found that sleep apnea was present in 95.7% of men and 65.9% of women at a cutoff of AHI > 10 events/hour, and that moderate to severe sleep apnea was present in 65.2% of men and 23.1% of women at an AHI cutoff of > 30 /hour. Although age was comparable between men and women, indices of central adiposity were substantially higher in men than women, as expected (*see* neck, waist, and sagittal girth in Table 1), and remained elevated even after these dimensions were normalized

TABLE 1. DISTRIBUTION OF ANTHROPOMETRIC AND SLEEP PARAMETERS IN SEVERELY OBESE MEN AND WOMEN

	Males ($n = 23$)		Females ($n = 91$)		P Value
	Mean	SD	Mean	SD	
Age, yr	40.9	8.9	41.9	9.3	0.653
Anthropometrics					
BMI, kg/m ²	51.5	7.5	49.1	0.9	0.207
Neck, cm	47.7	4.7	40.8	0.4	<0.001
Waist, cm	151.6	16.4	130.0	1.7	<0.001
Hip, cm	150.2	18.7	142.7	2.0	0.088
Waist-to-hip ratio	1.01	0.09	0.93	0.02	0.104
Girth, cm*	35.2	5.0	31.8	4.2	0.002
Sleep architecture					
Total sleep time, min	342.7	93.0	391.3	65.9	0.005
Sleep efficiency, %	81.1	13.7	85.4	11.7	0.129
Stage 1, %	24.5	19.6	13.7	13.3	0.002
Stage 2, %	57.4	16.9	60.6	11.3	0.280
Stage 3/4, %	5.0	7.1	11.1	9.2	0.004
Non-REM, %	87.0	9.7	85.4	7.5	0.406
REM, %	13.0	9.7	14.6	7.5	0.405
Apnea-hypopnea index, events/h					
Non-REM	54.1	38.2	23.6	32.9	<0.001
REM†	56.8	28.5	38.0	29.0	0.014
Total	54.6	36.1	26.4	31.6	<0.001
Baseline SaO ₂ , %					
Non-REM	95.0	2.4	95.8	1.6	0.062
REM†	93.6	5.9	95.1	2.6	0.101
Total	94.9	2.8	95.7	1.6	0.079
Average low SaO ₂ , %					
Non-REM	88.4	5.2	91.2	2.7	<0.001
REM†	84.7	8.5	88.8	5.6	0.012
Total	87.9	5.4	90.5	2.9	0.002
ΔSaO ₂ , %					
Non-REM	6.7	3.5	4.6	1.9	<0.001
REM†	8.9	4.8	6.2	3.6	0.010
Total	7.0	3.5	5.2	2.0	0.001
Ratio of apnea to total disordered breathing time					
Non-REM	0.33	0.31	0.18	0.23	0.003
REM†	0.40	0.36	0.23	0.28	0.034
Total	0.32	0.26	0.19	0.21	0.009

Definition of abbreviation: BMI = body mass index.

* Girth was measured in 78 women and 21 men.

† Twelve subjects (7 women and 5 men) had no REM sleep.

to stature (height; data not shown). In those with sleep apnea (AHI > 10 /h), sleep apnea was more severe in men than women (Table 2), as evidenced by significantly higher AHI, lower average low oxyhemoglobin saturation (SaO₂), larger desaturations (ΔSaO₂), and a greater proportion of complete apnea (vs. hypopnea). Using multiple linear regression, we found that the percentage of variability in AHI explained (R^2) by age, BMI, and neck circumference was estimated for males and females. In women, sleep apnea severity (AHI) correlated with BMI, age, and neck circumference. These factors each accounted for 7.5, 11.1, and 11.2% of the variability in AHI, respectively, and together accounted for 23.1% of the variability in AHI. In contrast, these parameters were not significantly associated with AHI in the men either singly or in combination, and could only account for 15.7% of the variability in AHI at maximum. These findings indicate that, despite marked variation in body weight and fat distribution, the most potent sleep apnea risk factors only predict a small proportion of the variability in sleep apnea severity, and suggest that underlying mechanisms linking sleep apnea and obesity remain to be elucidated.

In addition to obesity, hormonal status may impact on sleep apnea susceptibility, particularly in women. Postmenopausal women demonstrate increases in sleep apnea prevalence and severity compared with premenopausal women (36–40). Nevertheless, it is unclear whether female sex hormones protect obese women from developing sleep apnea, because conflicting responses to hormone replacement therapy have been observed in clinical and epidemiologic studies (41–43). Androgens appear to play a significant role in the pathogenesis of sleep apnea in obese women with polycystic ovarian disease, in whom the prevalence of sleep apnea well exceeds that in similarly obese women without this disorder (44). Moreover, the severity of sleep apnea in women with polycystic ovarian disease is related to the serum androgen concentrations (44), suggesting that male sex hormones promote the development of sleep apnea. Nevertheless, a substantial proportion of obese women are protected from the development and/or progression of sleep apnea (45), although the humoral mechanisms conferring protection remain largely unknown.

TABLE 2. SLEEP-DISORDERED BREATHING PARAMETERS IN MEN AND WOMEN WITH SLEEP APNEA*

	Males			Females			P Value
	n	Mean	SD	n	Mean	SD	
Apnea-hypopnea index, events/h							
Non-REM	20	61.6	7.8	47	41.9	5.5	0.049
REM	16	63.1	5.8	70	44.7	3.2	0.014
Total	22	57	7.5	60	37.5	4.4	0.025
Baseline SaO ₂ , %							
Non-REM	20	94.8	0.1	47	95.6	0.3	0.168
REM	16	93.1	1.5	70	94.8	0.3	0.084
Total	22	94.8	0.6	60	95.5	0.2	0.121
Average low SaO ₂ , %							
Non-REM	20	87.7	1.2	47	90.4	0.4	0.009
REM	16	83.7	2.1	70	88.2	0.7	0.013
Total	22	87.5	1.1	60	90.0	0.4	0.010
ΔSaO ₂ , %							
Non-REM	20	7.1	0.8	47	5.2	0.3	0.007
REM	16	9.4	1.2	70	6.7	0.4	0.014
Total	22	7.3	0.7	60	5.5	0.3	0.009
Ratio of apnea to total disordered breathing time							
Non-REM	18	0.42	0.07	45	0.23	0.04	0.010
REM	13	0.53	0.09	53	0.29	0.04	0.010
Total	16	0.36	0.06	53	0.23	0.03	0.059

* Apnea-hypopnea index > 10 episodes/hour.

Investigators have examined whether heritable factors can be implicated as determinants of sleep apnea susceptibility. Recent studies demonstrating familial aggregation and a racial predisposition to sleep apnea in individuals of African-American and Asian descent have suggested that heritable factors contribute to the development of sleep apnea (46–48) and to upper airway structural phenotypes (49). Further studies of the Cleveland Family Study cohort have demonstrated that sleep apnea (AHI) and obesity phenotypes are heritable (50). In further analyses, these investigators have demonstrated that AHI and BMI cosegregate. Obesity contributed substantially to the heritability of sleep apnea (51), and obesity accounted for the strongest associations between sleep apnea and specific genetic loci (52). Currently, the challenge in identifying distinct polymorphisms linked to sleep apnea may reflect the inherent phenotypic heterogeneity of this complex, polygenic disorder (53), rather than a lack of genotypic resolution. It will be necessary to establish specific intermediate traits that predispose or protect from sleep apnea before genetic markers of sleep apnea and obesity can be decoupled.

OBESITY AND UPPER AIRWAY NEUROMECHANICAL CONTROL

Modeling Upper Airway Function

Investigators have pointed to alterations in upper airway collapsibility during sleep as a key determinant of sleep apnea susceptibility. In early studies, upper airway collapsibility during sleep was found to vary along a continuum from health to disease (54–56). The severity of upper airway obstruction during sleep is related to quantitative differences in pharyngeal collapsibility, as reflected by elevations in the critical closing pressure (P_{crit}). Moreover, as P_{crit} fell below a minimally negative threshold of approximately -5 cm H_2O , sleep apnea remitted, suggesting that changes in P_{crit} play a pivotal role in the pathogenesis of this disorder (*see* Figure 1, *right*) (25, 57–61). In further studies, investigators have demonstrated that P_{crit} is determined by mechanical and neural factors that regulate pharyngeal collapsibility (62–67). Investigators measuring airway collapsibility in the absence of neuromuscular activity have demonstrated small, but consistent elevations in P_{crit} in patients with sleep apnea compared with normal subjects (68–70). These findings suggest that structural alterations predispose to upper airway obstruction during sleep when neuromuscular activity wanes (71). In further studies, investigators have demonstrated that structural defects may arise from soft tissues that compress the pharynx (72–75) and/or a loss of caudal traction on the upper airway from mediastinal, ribcage, and muscle attachments (63, 74, 76, 77).

In addition to alterations in upper airway structural control, disturbances in neuromuscular control play a role in sleep apnea pathogenesis. In general, upper airway obstruction elicits compensatory neuromuscular responses that maintain upper airway patency and prevent sleep apnea from developing. These responses can restore airway patency by recruiting muscles that dilate and elongate the airway (63, 65, 66, 67, 78–84). In patients with sleep apnea, impaired neural responses to airway obstruction account for the marked elevation in P_{crit} during sleep compared with normal individuals (54–56). A disturbance in neuromuscular control is further suggested by comparisons of critical pressures measured during sleep (54–56) with those assessed in paralyzed, anesthetized subjects (69, 85). P_{crit} increased from -13 cm H_2O during sleep to near zero (atmospheric) during neuromuscular blockade in normal subjects, which approaches levels observed in patients with sleep apnea

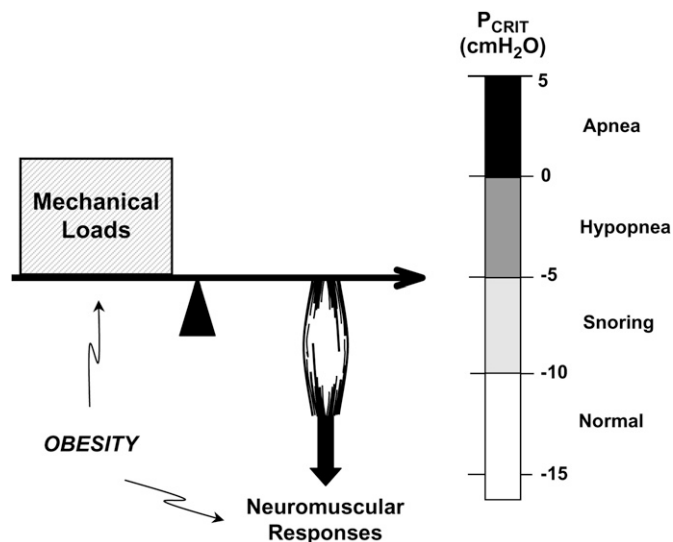


Figure 1. Obesity and the modulation of upper airway collapsibility and sleep apnea susceptibility. Upper airway collapsibility during sleep is represented by the critical pressure (P_{crit}), which spans a range from health (negative) to disease (positive). P_{crit} is determined by the mechanical loads imposed by bony structures and soft tissues on the pharynx, and are offset by neuromuscular responses to airway obstruction. Obesity can influence passive mechanical loads and neuromuscular control, thereby modulating upper airway collapsibility and sleep apnea susceptibility. *See* text for details.

both during sleep and while under anesthesia. More recently, methods have been developed for quantifying active neuromuscular responses in sleeping subjects, and a defect in these active responses has been demonstrated in patients with sleep apnea compared with normal subjects. This defect in neuromuscular control was independent of age, obesity, and sex (86), and may be caused by sleep-related reductions in dilator activity during sleep compared with wakefulness (87, 88) or by a loss of compensatory responses during sleep (87–99). Thus, current evidence indicates that sleep apnea is associated with fundamental disturbances in upper airway mechanical (68, 100, 101) and neuromuscular control (80, 102–106) (*see* Figure 1, *left*), and suggests that a combined defect is required to produce sleep apnea (86). Nevertheless, the impact of obesity on upper airway mechanical and neural properties has not been elucidated.

Mechanical Effects of Obesity

Obesity is associated with anatomic alterations that predispose to upper airway obstruction during sleep. These alterations may accrue from adiposity around the pharynx and torso as follows. First, increases in neck circumference and fat deposited around the upper airway (12, 72, 107–109) in obesity might narrow the upper airway. Second, upper airway collapsibility is higher in obese compared with nonobese individuals (25), and does not decrease appropriately when the pharynx is dilated by advancing the mandible anteriorly (110). Third, obesity and especially central obesity have been associated with reductions in lung volume (111), which leads to a loss of caudal traction on the upper airway, and an increase in pharyngeal collapsibility (63, 76–78, 84, 112, 113), increasing continuous positive airway pressure requirements (114) and a greater severity of sleep apnea (115). Thus, obesity imposes mechanical loads on both the upper airway and respiratory system that predispose to upper airway narrowing, collapse, and airflow obstruction during sleep (Figure 1). Although central adiposity is associated

with structural defects that compromise airway patency, the mechanisms causing these elevations in upper airway mechanical loads in obesity are not well understood.

Neuromuscular Effects of Obesity

Obesity may modulate upper airway neuromuscular control. Its effect is suggested by studies demonstrating improvements in critical pressure and sleep apnea after weight loss (25, 116). Central adiposity may lead to disturbances in neuromuscular control because men have a greater severity of sleep apnea in clinical and community-based cohorts than do women (1), and even lean men demonstrate subtle defects in upper airway neuromuscular responses to mechanical loads compared with lean women (87, 117–120). These findings are consistent with the notion that central obesity is associated with a marked blunting of upper airway neuromuscular responses (Figure 1), although the mechanisms linking regional adiposity and neural responses have not been delineated.

PUTATIVE ADIPOKINE MODULATORS OF UPPER AIRWAY FUNCTION

Obesity and sleep apnea are often associated with dysregulation of glucose and lipid metabolism (121–125), although the precise mechanisms for these associations are not well understood. In recent years, investigators have examined metabolic responses to excess caloric intake and have identified specific signaling factors responsible for disturbances in metabolic and upper airway control. As fat accumulates in adipose stores, it secretes humoral factors or adipokines that may influence upper airway function during sleep (126, 127). 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. In rodent models of obesity (128, 129), exogenous leptin leads to marked reductions in visceral and total body fat compared with diet-restricted pair-fed control animals (128, 129), whereas adiponectin reduces visceral adiposity selectively (130). In humans, leptin rises with increasing obesity, and is secreted preferentially by subcutaneous rather than visceral fat (131, 132), thus accounting for higher serum concentrations in women than men (133). In contrast, adiponectin rises steeply with weight loss (134), and especially with the loss of visceral adiposity (135, 136). Thus, leptin and adiponectin may lower sleep apnea susceptibility by reducing central adiposity and pharyngeal structural loads.

Obesity also induces an inflammatory state directly, because adipose tissue is an abundant source of proinflammatory cytokines, including tumor necrosis factor (TNF)- α , IL-6, and others (131, 132, 137, 138), as well as the profibrogenic adipokine leptin (139–141). 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 CO₂ ventilatory responses in mice (126, 142–144). Its action is antagonized by other adipose-related factors, namely the soluble leptin receptor (sOB-R) and C-reactive protein (CRP) (145), which bind circulating leptin and can decrease its central nervous system (CNS) uptake and action (145, 146). Levels of sOB-R and CRP are elevated in sleep apnea compared with matched control patients (147, 148) and decline with weight loss and the loss of visceral compared with central adiposity. Other adipokines, including TNF- α , (IL-1 β , and IL-6, are markedly elevated in obesity and especially in central obesity (131, 132, 147). Their somnogenic activity (149–153) may lead to a global depression on CNS activity and upper

airway neuromuscular control. As disturbances in upper airway neuromotor control ensue, increases in sleep apnea severity (154) can trigger further elevations in proinflammatory cytokines and exacerbate sleep apnea (147, 148, 155–160).

WEIGHT LOSS, SLEEP APNEA, AND UPPER AIRWAY FUNCTION

Weight loss remains a highly effective strategy for treating sleep apnea (25, 116, 161–168). In two controlled studies, investigators have demonstrated that a 10 to 15% reduction in body weight leads to an approximately 50% reduction in sleep apnea severity (AHI) in moderately obese male patients (25, 116). 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 (35, 169–172), and lead to an approximately 60% loss in excess body weight in the first 12 to 18 months postoperatively (173–185). In a recent meta-analysis of bariatric studies involving 22,094 patients, Buchwald and colleagues (11) have documented dramatic improvement in the vast majority of patients after surgery, with reductions in AHI of 33.9 episodes/hour (95% confidence interval [CI], 17.5–50.2 episodes/h) and sleep apnea resolution in 85.7% (95% CI, 79.2–92.2%) 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 (Pcrit) during sleep with weight loss (25, 116), which can be attributed to reductions in mechanical loads or improvements in pharyngeal neuromuscular control. These mechanisms may be related to alterations in humoral factors, including ghrelin, adiponectin, and leptin (134, 186–189), which have been linked to changes in body weight and regional adiposity. Of note, increases in ghrelin correlate with the amount of weight lost, whereas leptin, adiponectin, and endocannabinoids (190) can modulate the loss of weight from visceral and subcutaneous fat stores. Age-related variations in these neurohumoral factors may also account for the recurrence of sleep apnea over time even when substantial weight loss is maintained (191). Thus, it appears that humoral effects of circulating adipokines can influence weight loss patterns and adipokine profiles in regional adipose depots, which can account for wide variations in sleep apnea and upper airway responses to weight loss.

CONCLUSIONS

Obesity is a potent risk factor for the development and progression of sleep apnea (Figure 1). Its effect on sleep apnea susceptibility is related to the distribution of adiposity between the central and peripheral compartments. Central obesity accounts for the strong male predominance of this disorder, whereas peripheral adiposity may protect women from developing sleep apnea. Obesity and particularly central adiposity can increase sleep apnea susceptibility by increasing upper airway mechanical loads and/or decreasing compensatory neuromuscular responses. These effects may be mediated by circulating adipokines, which influence body fat distribution and CNS activity. As patients with sleep apnea lose weight, improvements in upper airway function and disease severity are likely related to the amount and patterns of weight loss as well as relative changes in protective and pathogenic adipokines.

Conflict of Interest Statement: None of the authors has a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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