Obesity and Obstructive Sleep Apnea
Pathogenic Mechanisms and Therapeutic Approaches

Alan R. Schwartz[1], Susheel P. Patil[1], Alison M. Laffan[1], Vsevolod Polotsky[1], Hartmut Schneider[1], and Philip L. Smith[1]

[1]Johns Hopkins School of Medicine Sleep Disorders Center, Baltimore, Maryland

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/m^3) and 30% (BMI > 30 kg/m^3) in overweight and obese adults, respectively (10). The NHANES data also demonstrate that the prevalence of severe obesity (BMI > 40 kg/m^2) 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/m^2), 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).

Correspondence and requests for reprints should be addressed to Alan R. Schwartz, M.D., Johns Hopkins Sleep Disorders Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224. E-mail: aschwar2@jhmi.edu

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 to stature (height; data not shown). In those with sleep apnea (AH1 > 10/h), sleep apnea was more severe in men than women (Table 2), as evidenced by significantly higher AHI, lower average low oxyhemoglobin saturation (Sa_{O_2}), larger desaturations (ΔSa_{O_2}), 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 1. DISTRIBUTION OF ANTHROPOMETRIC AND SLEEP PARAMETERS IN SEVERELY OBESE MEN AND WOMEN

	Males (*n = 23*)		Females (*n = 91*)		
	Mean	SD	Mean	SD	*P* Value
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 Sa_{O_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 Sa_{O_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
ΔSa_{O_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.

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

	Males			Females			
	n	Mean	SD	n	Mean	SD	*P* Value
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 Sa_{O_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 Sa_{O_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
ΔSa_{O_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.

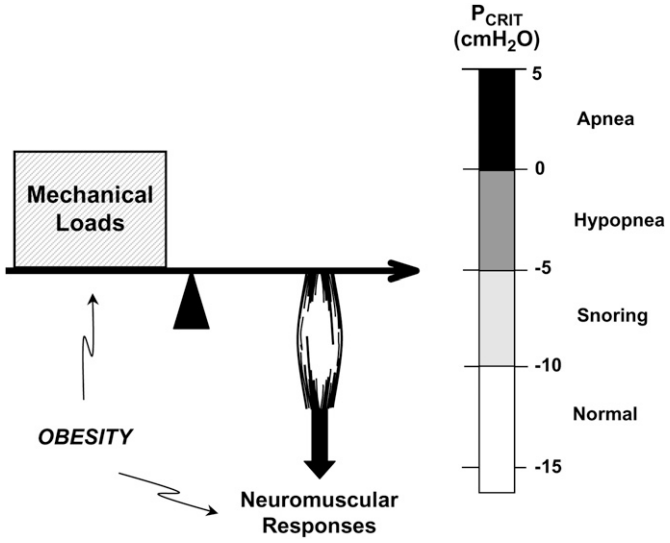

Figure 1. Obesity and the modulation of upper airway collapsibility and sleep apnea susceptibility. Upper airway collapsibility during sleep is represented by the critical pressure (Pcrit), which spans a range from health (negative) to disease (positive). Pcrit is determined by the mechanical loads imposed by boney 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.

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 (Pcrit). Moreover, as Pcrit fell below a minimally negative threshold of approximately -5 cm H_2O, sleep apnea remitted, suggesting that changes in Pcrit play a pivotal role in the pathogenesis of this disorder (*see* Figure 1, *right*) (25, 57–61). In further studies, investigators have demonstrated that Pcrit 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 Pcrit 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 Pcrit 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). Pcrit 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 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 CO_2 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-1β, 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 malabsorbtion, 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 endocannabanoids (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.

References

1. Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–1235.
2. Gastaut H, Tassinari CA, Duron B. Polygraphic study of diurnal and nocturnal (hypnic and respiratory) manifestations of Pickwick syndrome [in French]. *Rev Neurol (Paris)* 1965;112:568–579.
3. Punjabi NM, Sorkin JD, Katzel LI, Goldberg AP, Schwartz AR, Smith PL. Sleep-disordered breathing and insulin resistance in middle-aged and overweight men. *Am J Respir Crit Care Med* 2002;165:677–682.
4. Nieto FJ, Young TB, Lind BK, Shahar E, Samet JM, Redline S, D'Agostino RB, Newman AB, Lebowitz MD, Pickering TG. Association of sleep-disordered breathing, sleep apnea, and hypertension in a large community-based study. Sleep Heart Health Study. *JAMA* 2000;283:1829–1836.
5. Young T, Shahar E, Nieto FJ, Redline S, Newman AB, Gottlieb DJ, Walsleben JA, Finn L, Enright P, Samet JM. Predictors of sleep-disordered breathing in community-dwelling adults: the Sleep Heart Health Study. *Arch Intern Med* 2002;162:893–900.
6. Gold AR, Schwartz AR, Wise RA, Smith PL. Pulmonary function and respiratory chemosensitivity in moderately obese patients with sleep apnea. *Chest* 1993;103:1325–1329.
7. Burwell CS, Robin ED, Whaley RD, Bickelmann AG. Extreme obesity associated with alveolar hypoventilation: a Pickwickian syndrome. *Am J Med* 1956;21:811–818.
8. Hensrud DD, Klein S. Extreme obesity: a new medical crisis in the United States. *Mayo Clin Proc* 2006;81:S5–S10.
9. Wang Y, Beydoun MA. The obesity epidemic in the United States–gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev* 2007;29:6–28.
10. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among US adults, 1999–2000. *JAMA* 2002;288: 1723–1727.
11. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. *JAMA* 2004;292:1724–1737.
12. Davies RJ, Stradling JR. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. *Eur Respir J* 1990;3:509–514.
13. Shinohara E, Kihara S, Yamashita S, Yamane M, Nishida M, Arai T, Kotani K, Nakamura T, Takemura K, Matsuzawa Y. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *J Intern Med* 1997;241:11–18.
14. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. *Am J Respir Crit Care Med* 2002;165:1217–1239.
15. Young T, Peppard PE, Taheri S. Excess weight and sleep-disordered breathing. *J Appl Physiol* 2005;99:1592–1599.
16. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA* 2000;284:3015–3021.
17. Rajala R, Partinen M, Sane T, Pelkonen R, Huikuri K, Seppalainen AM. Obstructive sleep apnoea syndrome in morbidly obese patients. *J Intern Med* 1991;230:125–129.
18. Richman RM, Elliott LM, Burns CM, Bearpark HM, Steinbeck KS, Caterson ID. The prevalence of obstructive sleep apnoea in an obese female population. *Int J Obes Relat Metab Disord* 1994;18:173–177.
19. Vgontzas AN, Tan TL, Bixler EO, Martin LF, Shubert D, Kales A. Sleep apnea and sleep disruption in obese patients. *Arch Intern Med* 1994;154:1705–1711.
20. Davis G, Patel JA, Gagne DJ. Pulmonary considerations in obesity and the bariatric surgical patient. *Med Clin North Am* 2007;91:433–442.
21. Frey WC, Pilcher J. Obstructive sleep-related breathing disorders in patients evaluated for bariatric surgery. *Obes Surg* 2003;13:676–683.
22. Morrell MJ. Residual sleepiness in patients with optimally treated sleep apnea: a case for hypoxia-induced oxidative brain injury. *Sleep* 2004; 27:186–187.
23. O'Keeffe T, Patterson EJ. Evidence supporting routine polysomnography before bariatric surgery. *Obes Surg* 2004;14:23–26.
24. van Kralingen KW, de Kanter W, de Groot GH, Venmans BJ, van Boxem T, van Keimpema AR, Postmus PE. Assessment of sleep complaints and sleep-disordered breathing in a consecutive series of obese patients. *Respiration* 1999;66:312–316.
25. Schwartz AR, Gold AR, Schubert N, Stryzak A, Wise RA, Permutt S, Smith PL. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1991;144:494–498.
26. Peiser J, Lavie P, Ovnat A, Charuzi I. Sleep apnea syndrome in the morbidly obese as an indication for weight reduction surgery. *Ann Surg* 1984;199:112–115.
27. Strohl KP, Redline S. Recognition of obstructive sleep apnea. *Am J Respir Crit Care Med* 1996;154:279–289.
28. Vgontzas AN, Papanicolaou DA, Bixler EO, Hopper K, Lotsikas A, Lin HM, Kales A, Chrousos GP. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, and hypercytokinemia. *J Clin Endocrinol Metab* 2000;85:1151–1158.
29. Millman RP, Carlisle CC, McGarvey ST, Eveloff SE, Levinson PD. Body fat distribution and sleep apnea severity in women. *Chest* 1995;107:362–366.
30. Dancey DR, Hanly PJ, Soong C, Lee B, Shepard J Jr, Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. *Chest* 2003;123:1544–1550.
31. Ledoux M, Lambert J, Reeder BA, Despres JP. Correlation between cardiovascular disease risk factors and simple anthropometric measures. Canadian Heart Health Surveys Research Group. *CMAJ* 1997;157:S46–S53.
32. Legato MJ. Gender-specific aspects of obesity. *Int J Fertil Womens Med* 1997;42:184–197.
33. Guilleminault C, Stoohs R, Kim YD, Chervin R, Black J, Clerk A. Upper airway sleep-disordered breathing in women. *Ann Intern Med* 1995;122:493–501.
34. Newman AB, Foster G, Givelber R, Nieto FJ, Redline S, Young T. Progression and regression of sleep-disordered breathing with changes in weight: the sleep heart health study. *Arch Intern Med* 2005;165: 2408–2413.
35. Serafini FM, MacDowell AW, Rosemurgy AS, Strait T, Murr MM. Clinical predictors of sleep apnea in patients undergoing bariatric surgery. *Obes Surg* 2001;11:28–31.
36. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, Kales A. Prevalence of sleep-disordered breathing in women: effects of gender. *Am J Respir Crit Care Med* 2001;163:608–613.
37. Young T, Finn L, Austin D, Peterson A. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med* 2003;167:1181–1185.
38. Dancey DR, Hanly PJ, Soong C, Lee B, Hoffstein V. Impact of menopause on the prevalence and severity of sleep apnea 2. *Chest* 2001;120:151–155.
39. Anttalainen U, Saaresranta T, Aittokallio J, Kalleinen N, Vahlberg T, Virtanen I, Polo O. Impact of menopause on the manifestation and severity of sleep-disordered breathing. *Acta Obstet Gynecol Scand* 2006;85:1381–1388.
40. Resta O, Caratozzolo G, Pannacciulli N, Stefano A, Giliberti T, Carpagnano GE, De PG. Gender, age and menopause effects on the prevalence and the characteristics of obstructive sleep apnea in obesity. *Eur J Clin Invest* 2003;33:1084–1089.
41. Cistulli PA, Barnes DJ, Grunstein RR, Sullivan CE. Effect of short-term hormone replacement in the treatment of obstructive sleep apnoea in postmenopausal women. *Thorax* 1994;49:699–702.
42. Keefe DL, Watson R, Naftolin F. Hormone replacement therapy may alleviate sleep apnea in menopausal women: a pilot study. *Menopause* 1999;6:196–200.
43. Young T. Menopause, hormone replacement therapy, and sleep-disordered breathing: are we ready for the heat? *Am J Respir Crit Care Med* 2001;163:597–598.
44. Fogel RB, Malhotra A, Pillar G, Pittman SD, Dunaif A, White DP. Increased prevalence of obstructive sleep apnea syndrome in obese women with polycystic ovary syndrome. *J Clin Endocrinol Metab* 2001;86:1175–1180.
45. Carden K, Malhotra A. The debate about gender differences in obstructive sleep apnea. *Sleep Med* 2003;4:485–487.
46. Redline S, Tosteson T, Tishler PV, Carskadon MA, Millman RP, Milliman RP. Studies in the genetics of obstructive sleep apnea: familial aggregation of symptoms associated with sleep-related breathing disturbances. *Am Rev Respir Dis* 1992;145:440–444.
47. Redline S, Tishler PV, Hans MG, Tosteson TD, Strohl KP, Spry K. Racial differences in sleep-disordered breathing in African-Americans and Caucasians. *Am J Respir Crit Care Med* 1997;155:186–192. [Published erratum appears in *Am J Respir Crit Care Med* 1997;155:1820.]
48. Redline S, Tishler PV, Schluchter M, Aylor J, Clark K, Graham G. Risk factors for sleep-disordered breathing in children: associations with obesity, race, and respiratory problems. *Am J Respir Crit Care Med* 1999;159:1527–1532.
49. Schwab RJ, Pasirstein M, Kaplan L, Pierson R, Mackley A, Hachadoorian R, Arens R, Maislin G, Pack AI. Family aggregation of upper airway

soft tissue structures in normal subjects and patients with sleep apnea. *Am J Respir Crit Care Med* 2006;173:453–463.
50. Redline S, Tishler PV, Tosteson TD, Williamson J, Kump K, Browner I, Ferrette V, Krejci P. The familial aggregation of obstructive sleep apnea. *Am J Respir Crit Care Med* 1995;151:682–687.
51. Patel SR. Shared genetic risk factors for obstructive sleep apnea and obesity. *J Appl Physiol* 2005;99:1600–1606.
52. Palmer LJ, Buxbaum SG, Larkin E, Patel SR, Elston RC, Tishler PV, Redline S. A whole-genome scan for obstructive sleep apnea and obesity. *Am J Hum Genet* 2003;72:340–350.
53. Palmer LJ, Redline S. Genomic approaches to understanding obstructive sleep apnea. *Respir Physiolo Neurobiol* 2003;135:187–205.
54. Gleadhill IC, Schwartz AR, Schubert N, Wise RA, Permutt S, Smith PL. Upper airway collapsibility in snorers and in patients with obstructive hypopnea and apnea. *Am Rev Respir Dis* 1991;143:1300–1303.
55. Schwartz AR, Smith PL, Wise RA, Gold AR, Permutt S. Induction of upper airway occlusion in sleeping individuals with subatmospheric nasal pressure. *J Appl Physiol* 1988;64:535–542.
56. Smith PL, Wise RA, Gold AR, Schwartz AR, Permutt S. Upper airway pressure-flow relationships in obstructive sleep apnea. *J Appl Physiol* 1988;64:789–795.
57. Schwartz AR, Schubert N, Rothman W, Godley F, Marsh B, Eisele D, Nadeau J, Permutt L, Gleadhill I, Smith PL. Effect of uvulopalatopharyngoplasty on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis* 1992;145:527–532.
58. Winakur SJ, Smith PL, Schwartz AR. Pathophysiology and risk factors for obstructive sleep apnea. *Semin Respir Crit Care Med* 1998;19:99–112.
59. Schwartz AR, Bennett ML, Smith PL, De Backer WA, Hedner J, Boudewyns A, Van de Heyning PH, Ejnell H, Hochban W, Knaack L, *et al.* Therapeutic electrical stimulation of the hypoglossal nerve in obstructive sleep apnea. *Arch Otolaryngol Head Neck Surg* 2001;127:1216–1223.
60. Oliven A, Odeh M, Allan JJ, Smith PL, Schwartz AR. Electrical coactivation of tongue protrusors and retractors in patients with obstructive sleep apnea. *Sleep* 2002;25:A138–A139.
61. Oliven A, O'Hearn DJ, Boudewyns A, Odeh M, De Backer WA, Van de Heyning PH, Smith PL, Eisele DW, Allan L, Schneider H, *et al.* Upper airway response to electrical stimulation of the genioglossus in obstructive sleep apnea. *J Appl Physiol* 2003;95:2023–2029.
62. Schwartz AR, Thut D, Roach D, Smith PL. Effect of hypoglossal nerve stimulation on airflow mechanics in the isolated upper airway. *Am Rev Respir Dis* 1991;143:A405.
63. Thut DC, Schwartz AR, Roach D, Wise RA, Permutt S, Smith PL. Tracheal and neck position influence upper airway airflow dynamics by altering airway length. *J Appl Physiol* 1993;75:2084–2090.
64. Rowley JA, Williams BC, Smith PL, Schwartz AR. The effect of trachea displacement and hypercapnia on airflow dynamics in the upper airway. *Am J Respir Crit Care Med* 1995;151:A667.
65. Rowley JA, Williams BC, Smith PL, Schwartz AR. Neuromuscular activity and upper airway collapsibility: mechanisms of action in the decerebrate cat. *Am J Respir Crit Care Med* 1997;156:515–521.
66. Seelagy MM, Schwartz AR, Russ DB, King ED, Wise RA, Smith PL. Reflex modulation of airflow dynamics through the upper airway. *J Appl Physiol* 1994;76:2692–2700.
67. Schwartz AR, Thut DC, Brower RG, Gauda EB, Roach D, Permutt S, Smith PL. Modulation of maximal inspiratory airflow by neuromuscular activity: effect of CO2. *J Appl Physiol* 1993;74:1597–1605.
68. Isono S, Tanaka A, Remmers JE, Nishino T. Comparison of static mechanics of passive pharynx between patients with obstructive sleep apnea and normal subjects [abstract]. *Am J Respir Crit Care Med* 1995;151:A667.
69. Eastwood PR, Szollosi I, Platt PR, Hillman DR. Comparison of upper airway collapse during general anaesthesia and sleep. *Lancet* 2002;359:1207–1209.
70. Eastwood PR, Szollosi I, Platt PR, Hillman DR. Collapsibility of the upper airway during anesthesia with isoflurane. *Anesthesiology* 2002;97:786–793.
71. Malhotra A, Huang Y, Fogel R, Lazic S, Pillar G, Jakab M, Kikinis R, White DP. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. *Am J Med* 2006;119:72.e9–72.e14.
72. Schwab RJ, Gupta KB, Gefter WB, Metzger LJ, Hoffman EA, Pack AI. Upper airway and soft tissue anatomy in normal subjects and patients with sleep-disordered breathing: significance of the lateral pharyngeal walls. *Am J Respir Crit Care Med* 1995;152:1673–1689.
73. Isono S, Tanaka A, Sho Y, Konno A, Nishino T. Advancement of the mandible improves velopharyngeal airway patency. *J Appl Physiol* 1995;79:2132–2138.
74. Kairaitis K, Byth K, Parikh R, Stavrinou R, Wheatley JR, Amis TC. Tracheal traction effects on upper airway patency in rabbits: the role of tissue pressure. *Sleep* 2007;30:179–186.
75. Schwartz AR, Kirkness J, Smith P. Extraluminal tissue pressure: what does it mean? *J Appl Physiol* 2006;100:5–6.
76. Van de Graaff WB. Thoracic influence on upper airway patency. *J Appl Physiol* 1988;65:2124–2131.
77. Van de Graaff WB. Thoracic traction on the trachea: mechanisms and magnitude. *J Appl Physiol* 1991;70:1328–1336.
78. Series F, Cormier Y, Couture J, Desmeules M. Changes in upper airway resistance with lung inflation and positive airway pressure. *J Appl Physiol* 1990;68:1075–1079.
79. Pillar G, Malhotra A, Fogel RB, Beauregard J, Slamowitz DI, Shea SA, White DP. Upper airway muscle responsiveness to rising PCO(2) during NREM sleep. *J Appl Physiol* 2000;89:1275–1282.
80. Malhotra A, Fogel RB, Edwards JK, Shea SA, White DP. Local mechanisms drive genioglossus activation in obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;161:1746–1749.
81. Ryan S, McNicholas WT, O'Regan RG, Nolan P. Reflex respiratory response to changes in upper airway pressure in the anaesthetized rat. *J Physiol* 2001;537:251–265.
82. Series F, Demoule A, Marc I, Sanfacon C, Derenne JP, Similowski T. Inspiratory flow dynamics during phrenic nerve stimulation in awake normals during nasal breathing. *Am J Respir Crit Care Med* 1999;160:614–620.
83. Feroah TR, Forster HV, Pan L, Schlick NE, Martino P, Rice T. Negative pressure effects on mechanically opposing pharyngeal muscles in awake and sleeping goats. *J Appl Physiol* 2001;91:2289–2297.
84. Rowley JA, Permutt S, Willey S, Smith PL, Schwartz AR. Effect of tracheal and tongue displacement on upper airway airflow dynamics. *J Appl Physiol* 1996;80:2171–2178.
85. Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of the pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol* 1997;82:1319–1326.
86. Patil SP, Schneider H, Marx JJ, Gladmon E, Schwartz AR, Smith PL. Neuromechanical control of upper airway patency during sleep. *J Appl Physiol* 2007;102:547–556.
87. Pillar G, Malhotra A, Fogel R, Beauregard J, Schnall R, White DP. Airway mechanics and ventilation in response to resistive loading during sleep: influence of gender. *Am J Respir Crit Care Med* 2000;162:1627–1632.
88. Gleeson K, Zwillich CW, Bendrick TW, White DP. Effect of inspiratory nasal loading on pharyngeal resistance. *J Appl Physiol* 1986;60:1882–1886.
89. Van Lunteren E, Van de Graaff WB, Parker DM, Mitra J, Haxhiu MA, Strohl KP, Cherniack NS. Nasal and laryngeal reflex responses to negative upper airway pressure. *J Appl Physiol* 1984;56:746–752.
90. Brouillette RT, Thach BT. A neuromuscular mechanism maintaining extrathoracic airway patency. *J Appl Physiol* 1979;46:772–779.
91. Aronson RM, Onal E, Carley DW, Lopata M. Upper airway and respiratory muscle responses to continuous negative airway pressure. *J Appl Physiol* 1989;66:1373–1382.
92. Kuna ST, Smickley J. Response of genioglossus muscle activity to nasal airway occlusion in normal sleeping adults. *J Appl Physiol* 1988;64:347–353.
93. Sanna A, Veriter C, Kurtansky A, Stanescu D. Contraction and relaxation of upper airway muscles during expiratory application of negative pressure at the mouth. *Sleep* 1994;17:220–225.
94. Wheatley JR, Mezzanotte WS, Tangel DJ, White DP. Influence of sleep on genioglossus muscle activation by negative pressure in normal men. *Am Rev Respir Dis* 1993;148:597–605.
95. Sanna A, Veriter C, Stanescu D. Upper airway obstruction induced by negative-pressure ventilation in awake healthy subjects. *J Appl Physiol* 1993;75:546–552.
96. Mathew OP. Upper airway negative-pressure effects on respiratory activity of upper airway muscles. *J Appl Physiol* 1984;56:500–505.
97. Mathew OP, bu-Osba YK, Thach BT. Influence of upper airway pressure changes on genioglossus muscle respiratory activity. *J Appl Physiol* 1982;52:438–444.
98. Philip-Joet F, Marc I, Series F. Effects of genioglossal response to negative airway pressure on upper airway collapsibility during sleep. *J Appl Physiol* 1996;80:1466–1474.
99. Pillar G, Fogel RB, Malhotra A, Beauregard J, Edwards JK, Shea SA, White DP. Genioglossal inspiratory activation: central respiratory vs mechanoreceptive influences. *Respir Physiol* 2001;127:23–38.
100. Mezzanotte WS, Tangel DJ, White DP. Waking genioglossal electromyogram in sleep apnea patients versus normal controls (a neuromuscular compensatory mechanism). *J Clin Invest* 1992;89:1571–1579.

101. Fogel RB, Malhotra A, Shea SA, Edwards JK, White DP. Reduced genioglossal activity with upper airway anesthesia in awake patients with OSA. *J Appl Physiol* 2000;88:1346–1354.
102. Malhotra A, Pillar G, Fogel RB, Beauregard J, Edwards JK, Slamowitz DI, Shea SA, White DP. Genioglossal but not palatal muscle activity relates closely to pharyngeal pressure. *Am J Respir Crit Care Med* 2000; 162:1058–1062.
103. Berry RB, White DP, Roper J, Pillar G, Fogel RB, Stanchina M, Malhotra A. Awake negative pressure reflex response of the genioglossus in OSA patients and normal subjects. *J Appl Physiol* 2003;94: 1875–1882.
104. Fogel RB, Trinder J, White DP, Malhotra A, Raneri J, Schory K, Kleverlaan D, Pierce RJ. The effect of sleep onset on upper airway muscle activity in patients with sleep apnoea versus controls. *J Physiol* 2005;564:549–562.
105. Malhotra A, Pillar G, Fogel RB, Edwards JK, Ayas N, Akahoshi T, Hess D, White DP. Pharyngeal pressure and flow effects on genioglossus activation in normal subjects. *Am J Respir Crit Care Med* 2002;165:71–77.
106. Stanchina ML, Malhotra A, Fogel RB, Ayas N, Edwards JK, Schory K, White DP. Genioglossus muscle responsiveness to chemical and mechanical stimuli during non-rapid eye movement sleep. *Am J Respir Crit Care Med* 2002;165:945–949.
107. Denson SE, Taussig LM, Pond GD. Intraluminal tracheal cyst producing airway obstruction in the newborn infant. *J Pediatr* 1976;88:521–522.
108. Schwab RJ, Gefter WB, Hoffman EA, Gupta KB, Pack AI. Dynamic upper airway imaging during awake respiration in normal subjects and patients with sleep disordered breathing. *Am Rev Respir Dis* 1993;148:1385–1400.
109. Koenig JS, Thach BT. Effects of mass loading on the upper airway. *J Appl Physiol* 1988;64:2294–2299.
110. Isono S, Tanaka A, Tagaito Y, Sho Y, Nishino T. Pharyngeal patency in response to advancement of the mandible in obese anesthetized persons. *Anesthesiology* 1997;87:1055–1062.
111. Sharp JT, Henry JP, Sweany SK, Meadows WR, Pietras RJ. Effects of mass loading the respiratory system in man. *J Appl Physiol* 1964;19: 959–966.
112. Series F, Marc I. Influence of lung volume dependence of upper airway resistance during continuous negative airway pressure. *J Appl Physiol* 1994;77:840–844.
113. Series F, Cormier Y, Desmeules M. Influence of passive changes of lung volume on upper airways. *J Appl Physiol* 1990;68:2159–2164.
114. Heinzer RC, Stanchina ML, Malhotra A, Fogel RB, Patel SR, Jordan AS, Schory K, White DP. Lung volume and continuous positive airway pressure requirements in obstructive sleep apnea. *Am J Respir Crit Care Med* 2005;172:114–117.
115. Brown IG, Bradley TD, Phillipson EA, Zamel N, Hoffstein V. Pharyngeal compliance in snoring subjects with and without obstructive sleep apnea. *Am Rev Respir Dis* 1985;132:211–215.
116. Smith PL, Gold AR, Meyers DA, Haponik EF, Bleecker ER. Weight loss in mildly to moderately obese patients with obstructive sleep apnea. *Ann Intern Med* 1985;103:850–855.
117. O'Donnell CP, Schwartz AR, Smith PL. Upper airway collapsibility: the importance of gender and adiposity. *Am J Respir Crit Care Med* 2000;162:1606–1607.
118. Leech JA, Onal E, Dulberg C, Lopata MA. A comparison of men and women with occlusive sleep apnea syndrome. *Chest* 1988;94:983–988.
119. Mohsenin V. Gender differences in the expression of sleep-disordered breathing: role of upper airway dimensions. *Chest* 2001;120:1442–1447.
120. O'Connor C, Thornley KS, Hanly PJ. Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med* 2000;161:1465–1472.
121. Basta M, Vgontzas AN. Metabolic abnormalities in obesity and sleep apnea are in a continuum. *Sleep Med* 2007;8:5–7.
122. Gruber A, Horwood F, Sithole J, Ali NJ, Idris I. Obstructive sleep apnoea is independently associated with the metabolic syndrome but not insulin resistance state. *Cardiovasc Diabetol* 2006;5:22.
123. Lam JC, Lam B, Lam CL, Fong D, Wang JK, Tse HF, Lam KS, Ip MS. Obstructive sleep apnea and the metabolic syndrome in community-based Chinese adults in Hong Kong. *Respir Med* 2006;100:980–987.
124. McArdle N, Hillman D, Beilin L, Watts G. Metabolic risk factors for vascular disease in obstructive sleep apnea: a matched controlled study. *Am J Respir Crit Care Med* 2007;175:190–195.
125. Teramoto S, Yamamoto H, Yamaguchi Y, Namba R, Ouchi Y. Obstructive sleep apnea causes systemic inflammation and metabolic syndrome. *Chest* 2005;127:1074–1075.
126. Fruhbeck G, Gomez-Ambrosi J, Muruzabal FJ, Burrell MA. The adipocyte: a model for integration of endocrine and metabolic signaling in energy metabolism regulation. *Am J Physiol Endocrinol Metab* 2001;280:E827–E847.
127. Zhang HH, Kumar S, Barnett AH, Eggo MC. Dexamethasone inhibits tumor necrosis factor-alpha-induced apoptosis and interleukin-1 beta release in human subcutaneous adipocytes and preadipocytes. *J Clin Endocrinol Metab* 2001;86:2817–2825.
128. Barzilai N, Wang J, Massilon D, Vuguin P, Hawkins M, Rossetti L. Leptin selectively decreases visceral adiposity and enhances insulin action. *J Clin Invest* 1997;100:3105–3110.
129. Breslow MJ, Min-Lee K, Brown DR, Chacko VP, Palmer D, Berkowitz DE. Effect of leptin deficiency on metabolic rate in ob/ob mice. *Am J Physiol* 1999;276:E443–E449.
130. Masaki T, Chiba S, Yasuda T, Tsubone T, Kakuma T, Shimomura I, Funahashi T, Matsuzawa Y, Yoshimatsu H. Peripheral, but not central, administration of adiponectin reduces visceral adiposity and upregulates the expression of uncoupling protein in agouti yellow (Ay/a) obese mice. *Diabetes* 2003;52:2266–2273.
131. Arner P. Regional differences in protein production by human adipose tissue. *Biochem Soc Trans* 2001;29:72–75.
132. Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of the proteins secreted by the adipocytes in human subcutaneous and visceral adipose tissues. *Biochim Biophys Acta* 2000;1500:88–96.
133. Minocci A, Savia G, Lucantoni R, Berselli ME, Tagliaferri M, Calo G, Petroni ML, de Medici C, Viberti GC, Liuzzi A. Leptin plasma concentrations are dependent on body fat distribution in obese patients. *Int J Obes Relat Metab Disord* 2000;24:1139–1144.
134. Holdstock C, Engstrom BE, Ohrvall M, Lind L, Sundbom M, Karlsson FA. Ghrelin and adipose tissue regulatory peptides: effect of gastric bypass surgery in obese humans. *J Clin Endocrinol Metab* 2003;88: 3177–3183.
135. Gavrila A, Chan JL, Yiannakouris N, Kontogianni M, Miller LC, Orlova C, Mantzoros CS. Serum adiponectin levels are inversely associated with overall and central fat distribution but are not directly regulated by acute fasting or leptin administration in humans: cross-sectional and interventional studies. *J Clin Endocrinol Metab* 2003;88:4823–4831.
136. Staiger H, Tschritter O, Machann J, Thamer C, Fritsche A, Maerker E, Schick F, Haring HU, Stumvoll M. Relationship of serum adiponectin and leptin concentrations with body fat distribution in humans. *Obes Res* 2003;11:368–372.
137. Fried SK, Bunkin DA, Greenberg AS. Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol Metab* 1998;83:847–850.
138. Hotamisligil GS, Shargill NS, Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance. *Science* 1993;259:87–91.
139. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *N Engl J Med* 1996;334:292–295.
140. Tang M, Potter JJ, Mezey E. Leptin enhances the effect of transforming growth factor beta in increasing type I collagen formation. *Biochem Biophys Res Commun* 2002;297:906–911.
141. Marra F. Leptin and liver fibrosis: a matter of fat. *Gastroenterology* 2002;122:1529–1532.
142. Fruhbeck G, Gomez-Ambrosi J. Depot-specific differences in the lipolytic effect of leptin on isolated white adipocytes. *Med Sci Monit* 2002;8:BR47–BR55.
143. Shuldiner AR, Yang R, Gong DW. Resistin, obesity and insulin resistance–the emerging role of the adipocyte as an endocrine organ. *N Engl J Med* 2001;345:1345–1346.
144. Spiegelman BM, Flier JS. Obesity and the regulation of energy balance. *Cell* 2001;104:531–543.
145. Chen K, Li F, Li J, Cai H, Strom S, Bisello A, Kelley DE, Friedman-Einat M, Skibinski GA, McCrory MA, *et al.* Induction of leptin resistance through direct interaction of C-reactive protein with leptin. *Nat Med* 2006;12:425–432.
146. Brabant G, Horn R, von zur Mühlen A, Mayr B, Wurster U, Heidenreich F, Schnabel D, Gruters-Kieslich A, Zimmermann-Belsing T, Feldt-Rasmussen U. Free and protein bound leptin are distinct and independently controlled factors in energy regulation. *Diabetologia* 2000;43:438–442.
147. Manzella D, Parillo M, Razzino T, Gnasso P, Buonanno S, Gargiulo A, Caputi M, Paolisso G. Soluble leptin receptor and insulin resistance

as determinant of sleep apnea. *Int J Obes Relat Metab Disord* 2002;26:370–375.
148. Punjabi NM, Beamer BA. C-reactive protein is associated with sleep disordered breathing independent of adiposity. *Sleep* 2007;30:29–34.
149. Fang J, Wang Y, Krueger JM. Effects of interleukin-1 beta on sleep are mediated by the type I receptor. *Am J Physiol* 1998;274:R655–R660.
150. Krueger JM, Fang J, Hansen MK, Zhang J, Obal F Jr. Humoral regulation of sleep. *News Physiol Sci* 1998;13:189–194.
151. Krueger JM, Obal FJ, Fang J, Kubota T, Taishi P. The role of cytokines in physiological sleep regulation. *Ann N Y AcadSci* 2001;933:211–221.
152. Takahashi S, Kapas L, Fang J, Krueger JM. Somnogenic relationships between tumor necrosis factor and interleukin-1. *Am J Physiol* 1999;276:R1132–R1140.
153. Opp MR. Cytokines and sleep. *Sleep Med Rev* 2005;9:355–364.
154. Vgontzas AN, Zoumakis E, Lin HM, Bixler EO, Trakada G, Chrousos GP. Marked decrease in sleepiness in patients with sleep apnea by etanercept, a tumor necrosis factor-alpha antagonist. *J Clin Endocrinol Metab* 2004;89:4409–4413.
155. Phipps PR, Starritt E, Caterson I, Grunstein RR. Association of serum leptin with hypoventilation in human obesity. *Thorax* 2002;57:75–76.
156. Phillips BG, Kato M, Narkiewicz K, Choe I, Somers VK. Increases in leptin levels, sympathetic drive, and weight gain in obstructive sleep apnea. *Am J Physiol Heart Circ Physiol* 2000;279:H234–H237.
157. Ozturk L, Unal M, Tamer L, Celikoglu F. The association of the severity of obstructive sleep apnea with plasma leptin levels. *Arch Otolaryngol Head Neck Surg* 2003;129:538–540.
158. Marik PE. Leptin, obesity, and obstructive sleep apnea. *Chest* 2000; 118:569–571.
159. Fitzpatrick M. Leptin and the obesity hypoventilation syndrome: a leap of faith? *Thorax* 2002;57:1–2.
160. Chin K, Shimizu K, Nakamura T, Narai N, Masuzaki H, Ogawa Y, Mishima M, Nakao K, Ohi M. Changes in intra-abdominal visceral fat and serum leptin levels in patients with obstructive sleep apnea syndrome following nasal continuous positive airway pressure therapy. *Circulation* 1999;100:706–712.
161. Aubert-Tulkens G, Culee C, Rodenstein DO. Cure of sleep apnea syndrome after long-term nasal continuous positive airway pressure therapy and weight loss. *Sleep* 1989;12:216–222.
162. Browman CP, Sampson MG, Yolles SF, Gujavarty KS, Weiler SJ, Walsleben JA, Hahn PM, Mitler MM. Obstructive sleep apnea and body weight. *Chest* 1984;85:435–438.
163. Dixon JB, Schachter LM, O'Brien PE. Polysomnography before and after weight loss in obese patients with severe sleep apnea. *Int J Obes (Lond)* 2005;29:1048–1054.
164. Harman EM, Wynne JW, Block AJ. The effect of weight loss on sleep-disordered breathing and oxygen desaturation in morbidly obese men. *Chest* 1982;82:291–294.
165. Morgenthaler TI, Kapen S, Lee-Chiong T, Alessi C, Boehlecke B, Brown T, Coleman J, Friedman L, Kapur V, Owens J, *et al.* Practice parameters for the medical therapy of obstructive sleep apnea. *Sleep* 2006;29:1031–1035.
166. Strobel RJ, Rosen RC. Obesity and weight loss in obstructive sleep apnea: a critical review. *Sleep* 1996;19:104–115.
167. Suratt PM, McTier RF, Findley LJ, Pohl SL, Wilhoit SC. Changes in breathing and the pharynx after weight loss in obstructive sleep apnea. *Chest* 1987;92:631–637.
168. Veasey SC, Guilleminault C, Strohl KP, Sanders MH, Ballard RD, Magalang UJ. Medical therapy for obstructive sleep apnea: a review by the Medical Therapy for Obstructive Sleep Apnea Task Force of the Standards of Practice Committee of the American Academy of Sleep Medicine. *Sleep* 2006;29:1036–1044.
169. Busetto L, Tregnaghi A, Bussolotto M, Sergi G, Beninca P, Ceccon A, Giantin V, Fiore D, Enzi G. Visceral fat loss evaluated by total body magnetic resonance imaging in obese women operated with laparascopic adjustable silicone gastric banding. *Int J Obes Relat Metab Disord* 2000;24:60–69.
170. Huerta S, DeShields S, Shpiner R, Li Z, Liu C, Sawicki M, Arteaga J, Livingston EH. Safety and efficacy of postoperative continuous positive airway pressure to prevent pulmonary complications after Roux-en-Y gastric bypass. *J Gastrointest Surg* 2002;6:354–358.
171. Cummings DE, Weigle DS, Frayo RS, Breen PA, Ma MK, Dellinger EP, Purnell JQ. Plasma ghrelin levels after diet-induced weight loss or gastric bypass surgery. *N Engl J Med* 2002;346:1623–1630.
172. Balsiger BM, Kennedy FP, Abu-Lebdeh HS, Collazo-Clavell M, Jensen MD, O'Brien T, Hensrud DD, Dinneen SF, Thompson GB, Que FG, *et al.* Prospective evaluation of Roux-en-Y gastric bypass as primary operation for medically complicated obesity. *Mayo Clin Proc* 2000;75:673–680.
173. Bouldin MJ, Ross LA, Sumrall CD, Loustalot FV, Low AK, Land KK. The effect of obesity surgery on obesity comorbidity. *Am J Med Sci* 2006;331:183–193.
174. Charuzi I, Lavie P, Peiser J, Peled R. Bariatric surgery in morbidly obese sleep-apnea patients: short- and long-term follow-up. *Am J Clin Nutr* 1992;55:594S–596S.
175. Charuzi I, Fraser D, Peiser J, Ovnat A, Lavie P. Sleep apnea syndrome in the morbidly obese undergoing bariatric surgery. *Gastroenterol Clin North Am* 1987;16:517–519.
176. Fritscher LG, Mottin CC, Canani S, Chatkin JM. Obesity and obstructive sleep apnea-hypopnea syndrome: the impact of bariatric surgery. *Obes Surg* 2007;17:95–99.
177. Haines KL, Nelson LG, Gonzalez R, Torrella T, Martin T, Kandil A, Dragotti R, Anderson WM, Gallagher SF, Murr MM. Objective evidence that bariatric surgery improves obesity-related obstructive sleep apnea. *Surgery* 2007;141:354–358.
178. Kalra M, Inge T. Effect of bariatric surgery on obstructive sleep apnoea in adolescents. *Paediatr Respir Rev* 2006;7:260–267.
179. Kushner RF, Noble CA. Long-term outcome of bariatric surgery: an interim analysis. *Mayo Clin Proc* 2006;81:S46–S51.
180. Lankford DA, Proctor CD, Richard R. Continuous positive airway pressure (CPAP) changes in bariatric surgery patients undergoing rapid weight loss. *Obes Surg* 2005;15:336–341.
181. Loube DI, Loube AA, Mitler MM. Weight loss for obstructive sleep apnea: the optimal therapy for obese patients. *J Am Diet Assoc* 1994;94:1291–1295.
182. Scheuller M, Weider D. Bariatric surgery for treatment of sleep apnea syndrome in 15 morbidly obese patients: long-term results. *Otolaryngol Head Neck Surg* 2001;125:299–302.
183. Spivak H, Hewitt MF, Onn A, Half EE. Weight loss and improvement of obesity-related illness in 500 US patients following laparoscopic adjustable gastric banding procedure. *Am J Surg* 2005;189:27–32.
184. Valencia-Flores M, Orea A, Herrera M, Santiago V, Rebollar V, Castano VA, Oseguera J, Pedroza J, Sumano J, Resendiz M, *et al.* Effect of bariatric surgery on obstructive sleep apnea and hypopnea syndrome, electrocardiogram, and pulmonary arterial pressure. *Obes Surg* 2004;14:755–762.
185. Verse T. Bariatric surgery for obstructive sleep apnea. *Chest* 2005;128: 485–487.
186. Li C, Ioffe E, Fidahusein N, Connolly E, Friedman JM. Absence of soluble leptin receptor in plasma from dbPas/dbPas and other db/db mice. *J Biol Chem* 1998;273:10078–10082.
187. Faraj M, Havel PJ, Phelis S, Blank D, Sniderman AD, Cianflone K. Plasma acylation-stimulating protein, adiponectin, leptin, and ghrelin before and after weight loss induced by gastric bypass surgery in morbidly obese subjects. *J Clin Endocrinol Metab* 2003;88:1594–1602.
188. Ott V, Fasshauer M, Dalski A, Meier B, Perwitz N, Klein HH, Tschop M, Klein J. Direct peripheral effects of ghrelin include suppression of adiponectin expression. *Horm Metab Res* 2002;34:640–645.
189. Whitson BA, Leslie DB, Kellogg TA, Maddaus MA, Buchwald H, Billington CJ, Ikramuddin S. Adipokine response in diabetics and nondiabetics following the Roux-en-Y gastric bypass: a preliminary study. *J Surg Res* 2007;142:295–300.
190. Lastra-Lastra G, Lastra-Gonzalez G, Manrique C. The endocannabinoid network: insight into the regulation of the neuroendocrine and metabolic systems. *J Cardiometabolic Syndr* 2007;2:53–58.
191. Pillar G, Peled R, Lavie P. Recurrence of sleep apnea without concomitant weight increase 7.5 years after weight reduction surgery. *Chest* 1994;106:1702–1704.