Interactions Between Obesity and Obstructive Sleep Apnea

Implications for Treatment

*Abel Romero-Corral, MD, MSc; Sean M. Caples, DO;
Francisco Lopez-Jimenez, MD, MSc; and Virend K. Somers, MD, PhD, FCCP*

Obstructive sleep apnea (OSA) adversely affects multiple organs and systems, with particular relevance to cardiovascular disease. Several conditions associated with OSA, such as high BP, insulin resistance, systemic inflammation, visceral fat deposition, and dyslipidemia, are also present in other conditions closely related to OSA, such as obesity and reduced sleep duration. Weight loss has been accompanied by improvement in characteristics related not only to obesity but to OSA as well, suggesting that weight loss might be a cornerstone of the treatment of both conditions. This review seeks to explore recent developments in understanding the interactions between body weight and OSA. Weight loss helps reduce OSA severity and attenuates the cardiometabolic abnormalities common to both diseases. Nevertheless, weight loss has been hard to achieve and maintain using conservative strategies. Since bariatric surgery has emerged as an alternative treatment of severe or complicated obesity, impressive results have often been seen with respect to sleep apnea severity and cardiometabolic disturbances. However, OSA is a complex condition, and treatment cannot be limited to any single symptom or feature of the disease. Rather, a multidisciplinary and integrated strategy is required to achieve effective and long-lasting therapeutic success.

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Abbreviations: AHI = apnea-hypopnea index; CPAP = continuous positive airway pressure; HDL = high-density lipoprotein; OSA = obstructive sleep apnea

Our understanding of the implications of obstructive sleep apnea (OSA) on disease pathophysiology has been evolving rapidly. OSA is thought to adversely affect multiple organs and systems and may be especially relevant to cardiovascular disease.^{1,2} It

has been implicated in the etiology of hypertension^{3,4} and in the progression of several established medical conditions such as congestive heart failure, atrial fibrillation, diabetes, and pulmonary hypertension.¹ However, whether OSA is causally linked to the development of these latter disease states remains to be proven.^{1,2}

In the adult population, the prevalence of OSA is estimated to be ~25%, and as high as 45% in obese subjects.⁵⁻¹⁰ Obesity predisposes to and potentiates OSA. The prevalence of OSA and its consequences are likely to increase in light of the current obesity epidemic. Recent estimates suggest that 60% of the adult population in industrialized countries is overweight (BMI ≥ 25 kg/m²) and at least 30% is obese

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Affiliations: From the Division of Cardiovascular Diseases, Department of Internal Medicine (Drs Romero-Corral, Lopez-Jimenez, and Somers) and the Division of Pulmonary and Critical Care Medicine (Dr Caples), Mayo Clinic College of Medicine, Mayo Foundation, Rochester, MN; and the Department of Internal Medicine (Dr Romero-Corral), Albert Einstein Medical Center, Philadelphia, PA.

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Correspondence to: Virend K. Somers, MD, PhD, Division of Cardiovascular Diseases, Domitilia 4-350, 200 First St SW, Rochester, MN 55905; e-mail: somers.virend@mayo.edu

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(BMI ≥ 30 kg/m²).¹¹ Sleep fragmentation is an important consequence of OSA; whether such interrupted sleep results in pathophysiologically similar mechanisms such as sleep deprivation is not known. Experimental sleep deprivation, as well as self-reported short sleep (< 6 h/night),¹²⁻¹⁵ have been linked to metabolic dysregulation independent of obesity and OSA, suggesting important interactions between these conditions and increasing the complexity of their treatment.

At present, continuous positive airway pressure (CPAP) is considered the mainstay of treatment of OSA. However, despite the benefits of CPAP therapy seen in numerous clinical trials,¹⁶ noncompliance is evident in a significant proportion of patients,^{17,18} suggesting that other therapies are needed.

With few exceptions, weight loss may be an effective therapy, especially in overweight and obese patients, who may comprise > 70% of subjects with OSA.¹⁹ Weight loss, especially through bariatric surgery, has been shown to reduce the severity and symptoms of OSA and sometimes, though not always, result in its complete resolution.²⁰ In addition, weight loss may elicit beneficial changes in cholesterol, insulin resistance, leptin, inflammatory markers, and endothelial function,^{21,22} abnormalities that are not only associated with OSA but also with obesity, experimental sleep deprivation, and self-reported short sleep.

EPIDEMIOLOGY OF OSA

The best prevalence estimates of OSA in the general population are derived from six large studies conducted worldwide. These studies suggest that approximately 25% of adults with a BMI between 25 kg/m² and 28 kg/m² have at least mild OSA (apnea-hypopnea index [AHI] ≥ 5).⁵⁻¹⁰ However, the prevalence of OSA varies according to gender (~30% in men and ~15% in women), age, and body weight. Men's risk for OSA is twofold-higher than that of women.⁶ Postmenopausal women are at higher risk for OSA than premenopausal women,⁷ suggesting a potential role for hormonal differences in OSA pathophysiology. OSA is also affected by age, as prevalence increases until age 65 years, when for unclear reasons the prevalence reaches a plateau.²³ Data also suggest that the interaction between body weight (measured using BMI) and OSA in elderly subjects might be different from that in younger adults. Janssen²⁴ followed 4,968 elderly subjects (≥ 65 years) for 9 years and showed that the risk of OSA was not different between overweight (BMI 25-29.9 kg/m²) and normal-weight (BMI 20-24.9 kg/m²) elderly subjects. However, these results might be explained by the poor diagnostic performance of BMI in detecting

an excess of body fat in the elderly.²⁵ These findings may also be relevant to the "obesity paradox," which relates to a better survival in overweight subjects when compared with normal-weight subjects,²⁶ findings that are beyond the scope of this review. However, because of the important interaction between OSA and body weight, this subject is discussed below in greater detail.

OBESITY AND OSA

Obesity is considered a major risk factor for the development and progression of OSA.^{8,19,20,27,28} The prevalence of OSA in obese or severely obese patients is nearly twice that of normal-weight adults. Furthermore, patients with mild OSA who gain 10% of their baseline weight are at a sixfold-increased risk of progression of OSA, and an equivalent weight loss can result in a more than 20% improvement in OSA severity.²⁵ Moreover, the higher prevalence of OSA in obese subjects is not limited to adults; recent data show that obese children have a 46% prevalence of OSA when compared with children seen in a general pediatric clinic (33%).²⁹ This finding is further aggravated by the obesity epidemic among children and adolescents.³⁰ In fact, there are data suggesting that children and adolescents with OSA have more than a sixfold-increased risk of having metabolic syndrome,³¹ when compared with children and adolescents without OSA. These findings highlight the need to develop screening and prevention for these conditions, even as early as in childhood.

It is possible that obesity may worsen OSA because of fat deposition at specific sites. Fat deposition in the tissues surrounding the upper airway appears to result in a smaller lumen and increased collapsibility of the upper airway, predisposing to apnea.^{32,33} Moreover, fat deposits around the thorax (truncal obesity) reduce chest compliance and functional residual capacity, and may increase oxygen demand.³⁴ Visceral obesity is common in subjects with OSA.³⁵ However, the relationship between OSA and obesity is complex. Although there is compelling evidence showing that obesity, as well as visceral obesity, may predispose to OSA, and that losing weight results in OSA improvement, recent studies suggest that OSA may itself cause weight gain.^{36,37} Factors such as reduced activity levels and increased appetite, particularly for refined carbohydrates, may conceivably contribute to weight gain in OSA patients.¹³ Whether OSA predisposes to preferential accumulation of visceral fat remains to be determined.³⁸ CPAP treatment of OSA reduces the amount of visceral fat (as measured by abdominal CT scanning), even in patients without significant weight loss.³⁹ Finally, there are data showing substantial overlap in genetic substrates between OSA

and obesity. Patel et al⁴⁰ reported a significant correlation between AHI and anthropomorphic adiposity measures (ranging from 0.57 to 0.61), suggesting that obesity could explain nearly 40% of the genetic variance in sleep apnea. In another study, Popko et al⁴¹ showed that polymorphisms (Arg/Arg and Gln/Arg when compared with Gln/Gln) of the leptin receptor, which is involved in energy homeostasis and body weight regulation, are significantly correlated with both OSA and obesity when compared with healthy controls. These studies suggest that genetic polymorphisms may influence both sleep apnea and obesity, and may be importantly interrelated in the development of these conditions.

OSA, SLEEP DEPRIVATION, AND METABOLIC DYSREGULATION

Several cardiometabolic alterations have been associated with OSA, independent of obesity and other potential confounders. Among the most important are glucose intolerance and insulin resistance, which are risk factors for the development of diabetes and cardiovascular disease.^{42,43} Moreover, OSA has been associated with a heightened systemic inflammatory state, as shown by increases in cytokines,^{38,44} serum amyloid A,⁴⁵ and, in some but not all studies, C-reactive protein.^{46,47} Subjects with OSA who received effective treatment with CPAP have shown improvement in some of these metabolic and inflammatory abnormalities.^{39,48}

Systemic inflammation has also been described in subjects with short sleep duration.⁴⁹ Population studies show a dose-response relationship between self-reported short sleep duration and increased body weight, suggesting that sleep duration may be an important regulator of body weight and metabolic and

endocrine function. These close interactions between obesity, sleep deprivation, and OSA (Fig 1) share the common pathophysiologic feature of metabolic dysregulation. Weight loss may improve all of these conditions and might constitute an important potential intervention for these patients. In fact, studies assessing changes in sleep architecture after weight loss achieved through bariatric surgery (gastric banding) suggest that, 1 year later, there are significant increases in rapid eye movement and slow-wave sleep, with reduced daytime sleepiness.⁵⁰

Other metabolic disturbances present in OSA that could potentially improve with weight loss include lipid abnormalities. OSA patients have been shown to have increased triglycerides, total cholesterol/high-density lipoprotein (HDL) ratio and low-density lipoprotein and lower HDL values.⁵¹ Intermittent hypoxia, a key feature of OSA, causes an increase in the liver content of triglycerides in mice.^{52,53} OSA patients may also have reduced HDL-mediated inhibition of low-density lipoprotein oxidation *ex vivo*.⁵⁴ The independent roles of OSA and obesity in these abnormalities remain unclear, but these measures may improve with weight loss achieved through diet and exercise, again speaking to a close interaction between these conditions (Fig 1).

Finally, hormones related to obesity, weight control, satiety, and energy expenditure may be altered in OSA. Leptin is a hormone produced by adipose tissue and binds to the ventral medial nucleus of the hypothalamus, known as the satiety center. Binding of leptin to this nucleus signals to the brain that the body has had enough to eat, a sensation of satiety.⁵⁵ Sleep deprivation in the short term inhibits leptin production, suggesting a potential mechanism for the early development of obesity.⁵⁶ Paradoxically, subjects with obesity have higher levels of leptin, likely due to

FIGURE 1. Interaction between obstructive sleep apnea, obesity, sleep deprivation, and metabolic abnormalities. HDL = high-density lipoprotein.

increased fat mass. This hyperleptinemia is believed to be accompanied by desensitized cellular responses to leptin so that the effect of leptin is not achieved.⁵⁷ Leptin also modulates ventilatory control, and may therefore be implicated in abnormal breathing patterns in obesity.⁵⁸⁻⁶⁰ Other adipokines, such as tumor necrosis factor α and interleukin-6, are also elevated in obesity and may be linked to depression of CNS activity and airway neuromuscular control, thus perhaps increasing OSA severity, which consequently triggers proinflammatory substances, creating a vicious circle.⁶⁰ Indeed, leptin levels in OSA patients are higher than would be expected because of the obesity alone,^{37,38} and leptin levels are reduced after as little as 4 days of CPAP use.³⁹ Another adipokine closely related to obesity and OSA is adiponectin.^{61,62} Increased levels of serum adiponectin have been shown to improve glucose and lipid metabolism and prevent inflammation and atherosclerosis. Adiponectin is low in obesity and also in OSA. Furthermore, adiponectin levels have been shown to increase with CPAP treatment, suggesting that treating OSA could potentially reduce the metabolic disturbances and potentially reduce cardiovascular risk.^{61,62} Ghrelin, a hormone produced by cells lining the stomach, stimulates appetite and is considered a counter-regulator to leptin.⁶³ Interestingly, ghrelin is increased during the night in obese subjects,⁶⁴ and reduced sleep⁶⁵ has been shown to increase the production of ghrelin, which ultimately stimulates appetite, and might lead to obesity and worsening of OSA.¹³

WEIGHT LOSS AS A TREATMENT OF OSA

Most studies assessing the effects of weight loss on OSA have had methodologic limitations, including lack of either randomization and/or a control group for comparisons, inadequate adjustment for potential confounders, and limited follow-up. Many of the more recent studies assessing weight loss on OSA severity and outcomes were in the context of bariatric surgery.

In the last few years, three randomized trials have addressed whether weight loss can improve OSA through nonsurgical treatments.^{66,67} Kajaste and colleagues,⁶⁶ using a cognitive-behavioral program and an initial low-calorie diet with ($n = 14$) or without ($n = 17$) additional CPAP therapy, followed 31 obese men for 2 years to assess changes in the severity of OSA. Patients had lost an average of 13.5% of their initial body weight at 6 and 12 months when compared with baseline, but at 24 months the weight loss had diminished to 9% when compared with baseline. At baseline, the oxygen desaturation index (desaturation events per hour of sleep exceeding 4% from baseline) was 51 ± 31 and was reduced to 23 ± 18 and

25 ± 23 at 6 and 12 months, respectively. After 24 months, patients began to regain the lost weight and the oxygen desaturation index began to increase (32 ± 26) but was still significantly lower when compared with baseline.⁶⁶ Interestingly, the group of patients in this study who also underwent CPAP therapy did not differ in weight loss or oxygen desaturation index when compared with patients without additional CPAP therapy, although adherence was not measured objectively. This randomized clinical trial suggests that weight loss in obese patients with OSA might be an important therapeutic intervention. However, as in most weight-loss programs, patients started to regain the lost weight after 2 years followed by a worsening of their OSA severity. In addition, patients never reached a “normal” oxygen desaturation index.

In the second trial, Lam et al⁶⁷ randomized 101 patients (79% men) with mild-to-moderate OSA to one of three treatment groups: (1) conservative measures (sleep hygiene) alone or (2) with the addition of CPAP or (3) with the addition of oral appliances. All overweight subjects (83% of the sample) were referred to a weight-reduction class. After 10 weeks, all three groups of patients lost an average of 1.5 kg. Only CPAP therapy was associated with improvements in OSA severity, daytime sleepiness, and quality-of-life measures. Firm conclusions cannot be drawn from these two studies, but they do highlight the problems of recidivism and limited efficacy that may diminish the value of some weight-loss programs.

Very recently, Tuomilehto and colleagues⁶⁸ randomized a small group of subjects (70% men, mean BMI 32 kg/m^2) with mild, mostly supine-position predominant OSA (mean AHI 10) to either a 600 to 800 kcal/day diet plus supervised lifestyle counseling or routine lifestyle counseling over 1 year of study. The treatment group was rigorously followed, with 14 visits over 1 year, each lasting 60 to 90 min. At 1 year, the treatment group lost just more than 10 kg of weight, associated with a reduction in AHI of 4, whereas the controls lost an average of 2.4 kg, without measurable changes in AHI.⁶⁸ Longer-term follow-up is needed to determine the durability of such lifestyle modifications, but the rigor of this protocol raises the issue of whether such costly and time-intensive programs are of value in those with milder OSA.

A longitudinal cohort study followed 2,968 men and women for 5 years to assess the effects of weight loss or weight gain on OSA severity.⁶⁹ Men were more likely to develop worsening OSA severity with a given increase in weight than were women. In adjusted models, men who gained at least 10 kg were five times more likely to have moderate-to-severe OSA when compared with women, in whom the risk increased

2.5 times. Conversely, a similar amount of weight loss was associated with a greater improvement in OSA severity in men, but to a lesser degree in women, suggesting that weight gain and weight loss could have different consequences for OSA severity in men vs women.

In earlier studies, from the 1980s and 1990s, improvements in OSA severity were reported consistently in subjects in whom weight loss had been achieved without surgery.⁷⁰⁻⁷⁹ In these studies, patients who had lost 9 to 18% of their initial body weight showed marked improvement in their AHI (47%-100%), suggesting that if patients were able to maintain the weight loss, the benefits in OSA severity and other metabolic and endocrine parameters would be sustained. However, this remains to be proven.

Probably because of the limited weight loss achieved with conservative therapy, more recent trials assessing weight loss and OSA severity have been in the context of bariatric surgery, which may result in dramatic weight reduction, often maintained for up to 10 years.⁸⁰ Obese patients undergoing bariatric surgery have shown a prevalence of OSA of > 70%.²⁰ These patients may or may not have had symptoms of OSA and often have other important comorbidities, such as diabetes, hypertension, and dyslipidemia.¹⁹ After bariatric surgery, significant improvement and occasionally even resolution of these comorbidities, as well as of OSA, have been noted. Table 1 displays some of the recent studies assessing weight loss through bariatric surgery, and associated changes in OSA severity.^{50,81-99} Overall, patients undergoing bariatric surgery (regardless of the type of intervention) showed an average reduction of 15 kg/m² in BMI and 36 events/hour in the AHI, suggesting that every 1 unit reduction in BMI translated to a reduction of 2.3 units in the AHI. These results are very similar to a recently published metaanalysis showing that an average reduction of 17.9 kg/m² (95% CI, 55.3-37.7 kg/m²) translates into a reduction of 38.2 in AHI (95% CI, 31.9-44.4 AHI).¹⁰⁰ However, as this metaanalysis also points out, despite showing a significant drop in the average AHI in most of the patients, OSA resolved completely (AHI < 5) in only 4% of subjects, and most continued to have at least moderate OSA.⁹⁸ Thus, persistence of some degree of OSA in many patients who undergo bariatric surgery can be expected because most of these subjects, despite significant reduction in weight, still remain overweight, if not obese.

Although bariatric surgery may be considered an “extreme measure” for shedding weight, it provides support for the concept that reduced body fatness translates into important improvements and even resolution of several harmful conditions, including

OSA. Some studies even relate bariatric surgery to better survival and fewer cardiovascular events at mid- and long-term follow-up.¹⁰¹⁻¹⁰³ However, bariatric surgery is not exempt from complications and the 30-day mortality has been reported to be as high as 2% and 4.6% at 1 year,¹⁰⁴ highlighting that for every patient, a careful balance between possible benefits and complications must be made. In addition, some questions regarding weight loss remain to be resolved. For example, does the presence of sleep apnea blunt the success of weight loss and/or promote weight gain late after surgery? Also not known is whether residual OSA after surgery depends on the persistence of visceral fat, or some other variable, after surgery. The timing of a repeat polysomnography following weight loss in patients with OSA is not certain, but could be conducted when weight has been stable for several months.

CPAP TREATMENT OF OSA

CPAP is considered the mainstay of treatment of OSA and has shown benefits in dozens of randomized controlled trials. These benefits include reducing daytime sleepiness, improving quality of life, and lowering blood pressure.¹⁰⁵ In addition, short-term data suggest that CPAP may possibly attenuate some of the cardiometabolic alterations that are present not only in OSA but common also to obesity and sleep deprivation. CPAP therapy has also been associated with reductions in visceral fat and total cholesterol and increased HDL.¹⁰⁶ As for OSA patients with concomitant type 2 diabetes, CPAP therapy has been linked to better glycemic control and improved insulin sensitivity, although these results have not been consistent.¹⁰⁷⁻¹⁰⁹ Finally, CPAP has been associated with attenuation in inflammatory biomarkers and perhaps even improved endothelial function. Indeed, observational studies have reported better survival and fewer cardiovascular events in patients treated with CPAP when compared with patients with poor CPAP adherence or those who remained untreated.^{18,110}

However, important questions regarding CPAP treatment remain unanswered. Most trials have involved male subjects, and therefore we have limited insight into how women may benefit from CPAP therapy. The benefits of CPAP therapy on metabolic parameters in subjects with mild and moderate OSA also remain unclear. CPAP therapeutic effects rely on patient compliance, which can be problematic.^{17,111,112} Most important, definitive evidence that CPAP prevents cardiovascular events and reduces mortality remains to be obtained. Only carefully designed large prospective studies will answer these important questions.

Table 1—Association Between Weight Loss Achieved By Bariatric Surgery and Obstructive Sleep Apnea Severity

Study	No. Patients	Follow-up, mo	Year of Study	Type of Surgery	BMI		Reduction (% Change)	AHI		Reduction (% Change)
					Baseline	Follow-up		Baseline	Follow-up	
Rasheid et al ⁸¹	11	3-21	1998-2001	GBP	62	40	−22 (−35.5)	56	23	−33 (−68.9)
Haines et al ⁸²	101	6-42	1998-2005	GBP	56	38	−18 (−22.2)	51	15	−35 (−70.6)
Valencia-Flores et al ⁸³	29	13.7	1999-2002	GBP	56.5	39.2	−17.3 (−30.7)	53.7	8.6	−45.1 (−83.9)
Lankford et al ⁸⁴	15	12	2002-NA	GBP	48	32	−16 (−33.4)	32	11	−21 (−65.7)
Dixon et al ⁵⁰	25	17	1999-2002	GBP	52.7	37.2	−15.5 (29.5)	61.6	13.4	−48.2 (−78.3)
Guardiano et al ⁸⁵	8	28	NA	GBP	49	34	−15 (−30.7)	55	14	−41 (−74.6)
Busetto et al ⁸⁶	17	17	NA	IGB	55.8	48.6	−7.2 (−12.9)	52.1	14	−38.1 (−73.2)
Charuzi et al ⁹¹	46	46	1978-1986	GBP and VBG	47.5	32.1	−15.4 (−32.5)	58.8	7.8	−51 (−86.8)
Scheuller et al ⁸⁸	15	12-144	NA	GBP and VBG	160 ^a	105 ^a	−55 ^b (−65.6)	97	11.3	−85.7 (−88.4)
Sugerman et al ⁸⁹	40	69.6	1980-1990	GBP, VBG, and HG	56	40	−16 (−28.6)	64	26	−38 (−59.4)
Pillar et al ⁹⁰	14	90	NA	GBP	45	35	−10 (−22.3)	40	24	−16 (−40)
Summers et al ⁹⁹	1	6	NA	VBG	54	37	−17 (−31.5)	40	<5	−36 (−90)
Lettieri et al ⁹⁸	24	12	2003-2005	GBP	51.0	32.1	−18.9 (−37.1)	47.9	24.5	−23.4 (−48.8)
Buchwald et al ⁹²	1195	~24	1990-2003	GBP, VBG, HG, and BPD	NA	NA	−14	NA	NA	−33
Angrisani et al ⁹³	1	60	2000	GBP and VBG	~43.4	~35.5	−7.9 (−28.3)	NA	<5	100% resolved
Skroubis et al ⁹⁴	4	29.3	1994-2005	GBP and BPD	~45	~26	−19 (−42.3)	NA	<5	100% resolved
Nelson et al ⁹⁵	9	21	1999-2005	GBP	51	37	−14 (−27.5)	NA	NA	77% resolved
Nelson et al ⁹⁶	85	12-148	1985-2004	GBP	61	37	−24 (−39.4)	NA	NA	48% resolved
Cleator et al ⁹⁷	20	12	1997-2002	Ileogastrostomy	42.3	36	−6.3 (−14.9)	NA	NA	85% improved

AHI = apnea-hypopnea index; BPD = biliopancreatic diversion; GBP = gastric bypass; HG = horizontal gastroplasty; IGB = intragastric balloon; NA = not available; VBG = vertical banded gastroplasty.

^akg.

CONCLUSIONS

Weight loss appears to confer benefits not only on OSA severity but also in terms of mitigating cardio-metabolic consequences related to both OSA and obesity. Unfortunately, weight loss through diet, exercise, and/or medications has been hard to achieve and maintain. Bariatric surgery may be an alternative treatment of severe or complicated obesity, and important and sometimes impressive changes have been noted in cardiovascular risk factors, metabolic markers, and OSA severity. In addition, CPAP therapy may contribute to the weight loss process and may also, in and of itself, improve some of the metabolic abnormalities characteristic of OSA and obesity. However, it is clear that treatment of OSA cannot be limited to any single strategy, but rather requires a multidisciplinary approach, effective provider-patient communications, and systematic long-term follow-up to achieve an effective and long-lasting therapeutic success.

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