

COMMENTARY

Up, down, or no change: weight gain as an unwanted side effect of CPAP for obstructive sleep apnea

Commentary on Quan SF, Budhiraja R, Clarke DP, et al. Impact of treatment with continuous positive airway pressure (CPAP) on weight in obstructive sleep apnea. *J Clin Sleep Med*. 2013;9(10):989–993. doi:10.5664/jcsm.3064

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One of the few indisputable facts in medicine is that obesity is involved in the pathogenesis of obstructive sleep apnea (OSA).¹ What has remained in dispute is why: Mechanisms that have been implicated include (1) infiltrations of fatty tissue into upper airway structures and the neck; (2) the phenotype of obesity, particularly as assessed by sagittal girth, which in general bears a stronger relationship to OSA than body mass index—an effect that appears to be mediated through the influence of obesity involving the trunk and abdominal viscera in reducing lung volumes and a consequent decrease in tracheal tug; (3) the actions of a variety of adipokines that are elevated in obesity (tumor necrosis factor- α , interleukin-1 β , and interleukin-6) and are thought to depress upper airway neuromuscular control; (4) resistance to leptin mediated by an increase in soluble leptin receptor and C-reactive protein, both of which bind leptin and create leptin resistance; and (5) a decrease in adiponectin, which affects the distribution of visceral adipose tissue.^{2,3} Moreover, there is a robust relationship demonstrated in multiple studies appearing in the bariatric surgical literature demonstrating that significant weight loss is associated with a decline in the severity of OSA or even its resolution.⁴

Those of us who practiced sleep medicine in the distant past assumed that effective treatment of OSA with positive airway pressure modalities would likely lead to weight loss; this was transmitted to patients as somewhat of an inducement to agree to positive airway pressure therapy and to maintain compliance and adherence going forward. We theorized that many of our patients with OSA would be relieved of excessive daytime sleepiness by effective treatment, and that would lead to greater physical activity and, perhaps, even some variety of an exercise program. This theory was later bolstered by work that demonstrated an increase in appetite, particularly for higher-calorie food items, was engendered by sleep deprivation—arguably a believable mechanism by which relieving the sleep deprivation induced by OSA should lead to decreased appetite.⁵

This line of reasoning motivated a number of subsequent reports that did little to settle the matter. In 2008, Redenius et al found no significant changes in body mass index with continuous positive airway pressure (CPAP) use in a retrospective study,⁶ while Takahashi et al reported a decrease in acylated ghrelin levels in

patients with OSA after CPAP treatment, the “hunger hormone” implicated in previous studies⁷ as one mechanism by which sleep deprivation resulted in weight gain. A spate of often contradictory studies followed: Those showing no change in weight included 2 smaller randomized controlled trials that, after 12 and 24 weeks of CPAP, found no change in weight, but they were perhaps underpowered,^{8,9} and a nonblinded randomized study of seemingly adequate power also demonstrated no change in weight after a median of 4 years of CPAP use.¹⁰ On the other side of the coin, a small low-quality study of 21 patients using CPAP found that those reporting adherence lost a significant amount of weight compared to those admitting to nonadherence.¹¹ Another small study, virtually contemporaneous with that of Quan et al, prospectively studied 40 patients (19 female) with mild or moderate OSA treated with CPAP.¹² They were randomly assigned to 1 of 2 groups: those (n = 18) who received only weekly calls reminding them to monitor their weight and another group receiving dietary self-monitoring and a structured self-help weight loss manual. Both groups were equally morbidly obese, and both had similar adherence to CPAP at 12 weeks (72% and 62%, respectively; days >4 hours). Both groups attained similar weight loss at 12 weeks, but interestingly, most (73%) of the subjects who were only reminded to weigh themselves achieved weight loss.

This was basically the confusing state of affairs until the landmark study by Quan et al,¹³ which is the subject of this commentary. These investigators utilized data from the Apnea Positive Pressure Long-Term Efficacy Study (APPLES), a prospective, randomized, double-blind sham-controlled clinical trial that involved the collaboration of 5 different sites in the United States.⁸ This was a robust study design involving a large cohort (n = 1,105) with apnea-hypopnea indices (AHI) ≥ 10 events/h; body weight was measured in a subset of 812 participants (both actively treated and sham controls) after a 6-month interval. Unfortunately, counseling patients on the benefits of CPAP using possible weight loss as one justification fell to the wayside: The study found an average of 0.35 ± 5.01 kg of weight gain in the CPAP cohort and 0.70 ± 4.03 kg of weight loss in the sham controls, a difference that was significant at the $P = .001$ level; moreover, the degree of weight gain correlated

with hours of CPAP use. Finally, participants who were able to achieve the Medicare-mandated CPAP use of ≥ 4 hours of use for $\geq 70\%$ of nights gained the most weight compared to those in the CPAP cohort who exhibited lesser degrees of adherence. This surprising (at least to many of us) result was independent of gender, race, age, degree of sleepiness, and even OSA severity.

Additional evidence followed: In 2015, a meta-analysis of 3,181 patients from 25 randomized trials confirmed that CPAP significantly increased weight and body mass index,¹⁴ and in 2016 possible mechanisms for weight gain were explored by Shechter in a systematic review.¹⁵ The culprits appeared to include reductions in resting or asleep metabolic rate and no demonstrable increase in exercise or physical activity, essentially, energy balance moving in the wrong direction. That same year Tachikawa et al performed a detailed assessment of energy metabolism in 63 participants after an initial diagnosis of OSA (apnea-hypopnea index ≥ 20 events/h) was made at baseline, CPAP initiation, and after 3 months of use.¹⁶ They found no change in physical activity, a decrease in basal metabolic rate, and an increase in self-reported caloric intake.

Unfortunately, the debate rages on. Last year, Ou et al reported data from the somewhat controversial Sleep Apnea Cardiovascular Endpoints (SAVE) trial, involving a post-hoc propensity-matched analysis of 2,483 adults (1,248 in the CPAP group and 1,235 in the control group) and found that long-term CPAP use (mean duration of follow-up, 3.78 ± 1.46 years) did not engender significant weight gain or loss.¹⁷ Of course, a post-hoc study is of lesser quality; moreover, the comorbidity of cardiovascular disease may well have affected energy balance in ways that would prevent weight gain. That same year a small study of 12 patients examining the effect of CPAP on body composition and weight demonstrated once again an increase in weight in patients treated with CPAP; paradoxically, they found that this was due to an increase in lean mass while fat mass actually decreased, and hypothesized that this indicated a favorable metabolic outcome.

In the end, what are we to conclude? It appears that CPAP treatment for OSA most frequently causes an increase in body weight, and the study by Quan et al provides the best evidence we have. How to counsel patients starting on CPAP? Honesty is the best policy; if they ask (as they often do) whether the treatment will help them lose weight, we must advise that the opposite may occur. With or without CPAP, they must decrease caloric intake and increase physical activity in order to achieve weight loss. While the introduction of CPAP was a breakthrough in the treatment of OSA, the report by Quan et al demonstrated that it has a potential cost: weight gain. Lawrence and Lee, authors of the 1955 play *Inherit the Wind* captured this paradox of technological progress succinctly when defense attorney Henry Drummond is made to say, "Gentlemen, progress has never been a bargain. You have to pay for it."

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