Published in final edited form as:

Obesity (Silver Spring). 2009 January ; 17(1): 84–91. doi:10.1038/oby.2008.485.

Effects of Maintained Weight Loss on Sleep Dynamics and Neck Morphology in Severely Obese Adults

Teri L. Hernandez¹, Robert D. Ballard², Kathleen M. Weil¹, Trudy Y. Shepard¹, Ann L. Scherzinger³, Elizabeth R. Stamm³, Teresa A. Sharp⁴, and Robert H. Eckel¹

¹ Division of Endocrinology, Metabolism, and Diabetes, University of Colorado Denver, Aurora, Colorado

² National Jewish Medical and Research Center, Denver, Colorado

³ Department of Radiology, University of Colorado Denver, Aurora, Colorado

⁴ Department of Pediatrics, University of Colorado Denver, Aurora, Colorado

Abstract

The goals of the study were to determine if moderate weight loss in severely obese adults resulted in 1) reduction in apnea/hypopnea index (AHI), 2) improved pharyngeal patency, 3) reduced total body oxygen consumption (VO_2) and carbon dioxide production (VCO_2) during sleep, and 4) improved sleep quality. The main outcome was the change in AHI from before to after weight loss. Fourteen severely obese ($\text{BMI} > 40 \text{ kg/m}^2$) patients (3 males, 11 females) completed a highly controlled weight reduction program which included 3 months of weight loss and 3 months of weight maintenance. At baseline and post-weight loss, patients underwent pulmonary function testing, polysomnography, and MRI to assess neck morphology. Weight decreased from $134 \pm 6.6 \text{ kg}$ to $118 \pm 6.1 \text{ kg}$ (mean $\pm$ SEM; $F=113.763$, $p<0.0001$). There was a significant reduction in the AHI between baseline and post-weight loss (SUBJECT, $F=11.11$, $p=0.007$). Moreover, patients with worse sleep disordered breathing (SDB) at baseline had the greatest improvements in AHI (GROUP, $F=9.00$, $p=0.005$). Reductions in VO_2 (285 ± 12 to $234 \pm 16 \text{ ml/min}$; $F=24.85$, $p<0.0001$) and VCO_2 (231 ± 9 to $186 \pm 12 \text{ ml/min}$; $F=27.74$, $p<0.0001$) were also observed, and pulmonary function testing showed improvements in spirometry parameters. Sleep studies revealed improved minimum SaO_2 ($83.4 \pm 6.1\%$ to $89.1 \pm 1.2\%$; $F=7.59$, $p=0.016$), and mean SaO_2 ($90.4 \pm 1.1\%$ to $93.8 \pm 1.0\%$; $F=6.89$, $p=0.022$), and a significant increase in the number of arousals (8.1 ± 1.4 at baseline, to 17.1 ± 3.0 after weight loss; $F=18.13$, $p=0.001$). In severely obese patients, even moderate weight loss ($\sim 10\%$) boasts substantial benefit in terms of the severity of SDB and sleep dynamics.

Keywords

Obesity; pharynx; diet; oxygen consumption; carbon dioxide production; AHI

INTRODUCTION

It is widely recognized that obesity is an important risk factor for obstructive sleep apnea (OSA) and sleep-disordered breathing (SDB). Depending on the report, approximately 10–50% of patients presenting for evaluation and therapy of obesity have concurrent OSA (1,2),

and while excessive daytime sleepiness (EDS) as part of SDB affects about 5% of the general population (3), it is a chief complaint of obese persons even in the absence of OSA (2,4). Obstructive sleep apnea, in particular, leads to disruption of sleep due to frequent arousals and awakenings that occur in response to recurrent complete or partial pharyngeal occlusions and associated hypoxemia (5). Both obese and non-obese patients with OSA therefore often complain of a lack of restoration from seemingly adequate nocturnal sleep and subsequent EDS (6). Recent evidence now provides a strong link between OSA and progression to ischemic heart disease, heart failure, and stroke (7), further underscoring the relationship between obesity and cardiovascular disease.

Patients with obesity can complain of disturbed sleep even in the absence of discrete OSA (8), and nocturnal sleep studies of obese patients have demonstrated lower sleep efficiency and more time spent awake (4). Seminal daytime nap studies have revealed reduced sleep latency and time awake in obese subjects without OSA (4), consistent with the presence of EDS. The sources of this sleep disruption remain under investigation. One contributor to sleep disruption might include an increased workload resulting from breathing through an anatomically narrowed upper airway during sleep, even in the absence of discrete apneas/hypopneas (9). Obesity is also associated with increases in small airway resistance and lung tissue resistance that seem to result from reduced lung volume (10). Moreover, chest wall and total respiratory system compliance are reduced in obesity, apparently due to compression of the thoracic cage, diaphragm, and lungs by excessive adipose tissue (11). Such mechanical changes could account for the 70% increase in work of breathing that has been observed during wakefulness in obese patients (12), which could also play a role in disrupting sleep. Finally, it has been suggested that circadian and/or metabolic abnormalities, such as visceral obesity, insulin resistance, and heightened levels of inflammatory cytokines, promote EDS (4,13), with insulin resistance being independently associated with OSA (13). The common concurrence of OSA and obesity has raised questions as to whether OSA is simply associated with obesity, or is a cause or effect of obesity (7).

We undertook this mechanistic, carefully designed study working under the hypothesis that sleep quality and sleep architecture would be favorably modified by weight loss in the severely obese. It was our intent to more clearly elucidate the underlying mechanisms mediated by weight loss pertaining to sleep quality and architecture in a small group of obese patients. The goals of the study were to determine if moderate weight loss in severely obese patients resulted in 1) a reduction in apnea/hypopnea index (AHI), 2) improved pharyngeal patency, 3) reduced total body oxygen consumption (VO_2) and carbon dioxide production (VCO_2) during sleep, and 4) improved sleep quality. The main outcome of this study was the change in AHI from before to after weight loss.

METHODS AND PROCEDURES

SUBJECTS

During the years 1998–2000, subjects were recruited from severely obese patients (BMI 40 kg/m^2) between 18–50 years of age referred to the weight reduction program at the University of Colorado Denver (UCD). Exclusions from participation included: diabetes, uncontrolled hypertension, cardiovascular disease, previously diagnosed OSA, OSA requiring treatment with continuous positive airway pressure, narcolepsy, chronic respiratory disease, and hypercapnia (PaCO_2 45 mmHg while awake) by arterial blood gases (indicative of obesity hypoventilation syndrome). Subjects were also excluded if they took medications that altered carbohydrate metabolism, sex hormones, antidepressants, and appetite suppressants. The Colorado Multiple Institutional Review Board approved this study and all subjects gave their written, informed consent.

PROTOCOL

Each subject was studied over 9 months, which included 7 phases: screening, baseline, weight loss, weight maintenance, diet phase I, washout, diet phase II. This protocol has been previously described (14). After providing informed consent, subjects participated in a screening visit for obtaining a history, physical examination, and blood tests that included a metabolic panel, complete blood count, arterial blood gas, and thyroid-stimulating hormone (TSH). Qualified subjects then entered the baseline phase, which required a 2-day/2-night stay on the Clinical Translational Research Center (CTRC) at UCD. Subjects had pulmonary function testing (PFT), a resting metabolic rate (RMR), and magnetic resonance imaging (MRI) of the upper airway during this stay. To measure oxygen consumption and carbon dioxide production, subjects were studied in a whole-room indirect calorimeter during both days between 3 pm and 7 am the following morning. Subjects were prepared for full polysomnography (described below) before entering the calorimeter, with the first night used as an acclimatization night followed by sleep data acquisition during the second chamber night (15). Although most room calorimeter studies involve a 24-hour stay, the duration for this study was reduced to a 16-hour period because of the potential for loss of sleep leads and patient discomfort related to a longer duration with the attachment of the sleep monitoring system components. In addition, as air-tight environment must be maintained for accurate measurement by the room calorimeter, it was not possible for sleep technicians to enter the room for lead repair if warranted. Based upon preliminary trials with the sleep monitoring system in the room calorimeter, we determined that the 16-hour period provided quality sleep and calorimetry data, with reasonable patient comfort.

Subjects then entered a 3-month weight loss program, using meal replacement products (Slim-Fast Food Products, West Palm Beach, FL) as their sole source of nutrition. Caloric restrictions varied from 1000–1500 kcal/d, as directed by initial body weight and resting metabolic rate, with a goal for subjects to lose between 5% and 15% of their baseline body weight. Subjects made weekly outpatient visits to the CTRC, when a study nurse and registered dietitian evaluated and counseled them for additional weight loss. After completing the weight loss program, subjects entered a 3-month, reduced-weight maintenance phase, during which they were permitted 2 mixed-food meals daily with additional Slim-Fast meal replacement products to allow an intake of 1500–2500 kcal/day, as determined by the study dietitian. During this phase, subjects again made weekly outpatient visits to the CTRC.

Upon completion of the reduced-weight maintenance phase, subjects were readmitted as out-patients to the CTRC for 17 days on 2 separate occasions. During those 17 days, patients were randomly provided 2 test diets (described in (14)). The differing diets were studied to address a secondary hypothesis. During the first stay the patients again underwent blood tests, PFT, MRI scan of the upper airway, and 2 sequential 16-hour stays in the whole-room calorimeter. Weekly during 3 months of weight loss and 3 months of weight-maintenance phase, perceived sleep quality was assessed using the Pittsburgh Sleep Quality Index (PSQI).

Whole-room Indirect Calorimetry—This was conducted in a dedicated 2.6×3.4 m chamber located on the GCRC. This sealed chamber contains a sleeping futon, desk, TV/video cassette player, and toilet. Meals and other necessities are provided via a sealed airlock. Methods employed for the measurement of oxygen consumption (VO_2) and carbon dioxide production (VCO_2) have previously been described in detail (16).

Resting Metabolic Rate—For the purposes of estimating energy intake and monitoring the effect of dietary composition on respiratory quotient (RQ), RMR measurements were

obtained before subjects were admitted to the whole-room calorimeter. Resting metabolic rate was measured by indirect calorimetry using a ventilated hood (Sensormedics Metabolic Cart, Model 2900, Yorba Linda, CA).

Laboratory Procedures—Serum insulin concentrations were measured by radioimmunoassay (17). Total cholesterol and triglycerides were measured enzymatically with a colorimetric endpoint (Roche Diagnostic Systems, Indianapolis, Indiana, USA), as were HDL cholesterol levels after precipitation with dextran sulfate/magnesium (Diagnostic Chemicals Ltd., Oxford, Connecticut, USA). Low-density lipoprotein (LDL) cholesterol was calculated using the equation of Friedewald et al. (18). Glucose was measured using a hexokinase method (Cobas Mira Plus, Diagnostic Chemicals Ltd, Oxford, Connecticut, USA).

Polysomnography—Polysomnography (PSG) for assessment of sleep-related parameters was recorded using Alice 3 (Respironics, version 1.20, Murrysville, PA) software and included the following physiologic parameters: Electroencephalogram (C4/A1, C3/A2, O1/A2), bilateral electro-oculogram, submental and tibial electromyograms, electrocardiogram (modified V2 lead), oronasal thermistor, piezo-crystal respiratory belts, snoring microphone, position sensor, and oxygen saturation via pulse-oximetry (Nellcor, Boulder, CO). Electrodes were positioned in triplicate to allow multiple options for continued data acquisition in the event of loss of signal from other recording electrodes. These signals were transferred via cable through a sealed cable port to a laptop PC (Omnibook, Hewlett Packard, Palo Alto, CA) located outside the calorimeter. Studies were subsequently scored using sleep staging criteria defined by Rechtschaffen and Kales (19) and respiratory scoring criteria proposed by the American Academy of Sleep Medicine (20).

Hypopnea events were determined as follows: at least a 50% reduction of airflow lasting at least 10 seconds, and a 3% reduction in oxygen saturation. When breathing ceased for >10 seconds, the event was considered apnea. The apnea/hypopnea index (AHI, described below) was calculated as: apnea events + hypopnea events per hour of sleep. The sleep technicians were not blinded to treatment (pre-vs. post-weight loss).

MRI scan—MR images were obtained using a 1.5T GE Sigma Horizon LX (GE Medical Systems, Milwaukee, WI) with subjects supine and their head in a neutral anatomic position, as defined by aligning the Frankfurt plane (defined by surface landmarks) perpendicular to the scanning table. Subjects breathed transnasally with mouth closed and were advised to not swallow during scanning. T1 weighted axial (TR = 600 ms, TE = 20 ms, 5 mm slice thickness) and sagittal (TR = 600 ms, TE = 15–20 ms, 3 mm slice thickness) scans were obtained to include all tissue to the skin line. Axial images were obtained from the top of the hard palate to the larynx, while sagittal images were centered about a midsagittal plane through the long axis of the airway. Images were electronically transferred to a workstation (Sun Microsystems, Mountain View, CA) for analysis following the techniques of Schwab and colleagues(21). The axial image with the smallest airway area was selected for analysis by a single observer with no reference to previous imaging. Areas were manually windowed and outlined using programs developed at the reading center using IDL development software (IDL Systems, Boulder, CO). Airway measurements made from axial views included cross-sectional area, anterior-posterior length, and transverse diameter of the airway. Soft tissue measures from axial views included subcutaneous lateral fat width, subcutaneous posterior fat width, pterygoid thickness, parapharyngeal fat pad width, parapharyngeal fat pad distance, lateral pharyngeal wall width, and intermandibular distance. Soft tissue measures from the sagittal views included soft palate anterior-posterior width, soft palate oblique width, soft palate vertical length, soft palate center length, soft palate area, tongue anterior-posterior diameter, tongue oblique width, tongue area, tongue

vertical dimension, tongue anterior-posterior dimension, mandible-soft palate distance, and mandible-posterior pharyngeal wall distance.

Pulmonary Function Tests—Spirometry and lung volume assessments for FEV were measured in an Autobox chamber (Model 6200, SensorMedics, Yorba Linda, CA). Calibrations were performed prior to each individual's testing. Normal values for comparison were established by Crapo and colleagues (22,23).

Pittsburgh Sleep Quality Index (PSQI)—The PSQI (24,25) is a 19-item, self-administered instrument which focuses on perceived sleep quality and impairment during the previous 4 weeks using a Likert-scale. The participants in this study completed the PSQI weekly throughout their weight loss and weight maintenance (7 time points). For this analysis, however, data from 3 time points were considered: baseline, after weight loss, and after weight maintenance. Six component areas were assessed: subjective sleep quality, latency, duration, efficiency, disturbances, and daytime dysfunction. A higher summary global score is indicative of poorer perceived sleep quality. Acceptable measures of internal consistency (Cronbach's $\alpha=0.83$), test-retest reliability (global score; $r=0.84$; $p<0.001$), and validity (distinct global score profiles demonstrated between 4 patient groups) have been established (25). A global PSQI score >5 has been shown to yield a diagnostic sensitivity of 89.6% and specificity of 86.5% ($\kappa=0.75$, $p<0.001$) in distinguishing "good" versus "poor" sleepers (25).

Statistical Analyses—Sample size determination for this study was based on data from the study of Smith et al. (26). In that study of 15 severely obese patients, when body weight decreased from 106.2 ± 7.3 kg (mean $\pm$ SEM) to 96.6 ± 5.9 kg, apnea frequency (the outcome variable) fell from 55.0 ± 7.5 to 20.2 ± 7.1 episodes/hour ($p<0.01$). Using $\alpha=0.05$ and power of 0.8, to detect a regression coefficient of 0.6 or more between weight loss and decrease in apnea frequency, it was determined that a sample size of 15 subjects was needed. Because the study by Smith et al. (26) was of patients with documented OSA, the sample size for this study was calculated assuming 1.5 times the standard deviation seen in the change in apnea frequency in the 1985 study.

Although there were 2 post-weight loss diet phases in the study protocol, there were no differences in the measured variables between the 2 phases (data not shown). For consistency, data for the "post-weight loss" endpoint are all from the high-carbohydrate diet phase. Data with non-normal distributions were log-transformed, and all assumptions for each test were met. Due to the number of analyses, but keeping in mind the small sample size, a p -value of 0.025 was considered to be significant. Analyses were run using SPSS, version 15.0 (Chicago, Illinois, USA).

Linear regression and ANOVA were used to test the main outcome, which was the difference in the apnea-hypopnea index (AHI) between baseline to after weight loss. The sleep and MRI outcomes outside of the main outcome were analyzed using ANOVA. For each of these analyses, the dependent variable was the difference in the outcome between baseline to after weight loss. For the ANOVA model, data were first analyzed using SUBJECT as a factor. Second, the data were analyzed using SUBJECT and GROUP (normal, mild, moderate OSA) as factors. Unless specifically described, there were no significant changes by GROUP in the 2-way ANOVA model. The GROUP category was determined using levels of OSA based on AHI, as determined by the American Academy of Sleep Medicine Task Force (20): Normal (<5 events/hour; $n=4$); Mild (5–15 events/hour; $n=7$); and Moderate (15–30 events/hour; $n=3$). There was 1 male participant in each AHI group.

Analysis of variance with repeated measures (3 time points: baseline, post-weight loss; post-weight maintenance) was used to assess changes in perceived sleep quality over time, with the global PSQI score as the dependent variable.

RESULTS

Sixteen patients completed the entire protocol. However, 1 patient did not achieve or maintain the desired weight loss. We additionally removed 1 patient from the analysis who had an AHI >30 events per hour, and thus had severe OSA according to published standards (20). Two patients were missing the baseline MRI measurements due to equipment mechanical difficulties, but were otherwise included in the analysis. The final number of patients included in this analysis was $n=14$ (3 males and 11 females); comparisons between baseline and post-weight loss for neck morphology used $n=12$. The AHI in these patients was characterized by more episodes of hypopnea than apnea. Data in Table 1 are presented as mean $\pm$ SD, and all other data are presented as mean $\pm$ SEM.

Mean weight was reduced from 134.0 ± 6.6 kg to 117.7 ± 6.1 kg ($F=113.763$, $p<0.0001$) at the time of the 17-day CTSC admission for the HC diet. As seen in Figure 1, weight loss was well-maintained throughout the remainder of the study after the 3-month weight reduction program. Statistical analyses revealed no significant differences in weight or sleep characteristics between the HC and HF diet admissions to the CTSC (data not shown). Variables are presented as “change in” to mean the change between baseline and post-weight loss.

Apnea-Hypopnea Index—In the regression model, neither the baseline weight, nor the change in weight was found to be a predictor of the change in AHI. Similarly, 1-way ANOVA by SUBJECT showed no significant difference in AHI between baseline and post-weight loss. However, when the data were further analyzed using 2-way ANOVA with factors SUBJECT and GROUP, there was a significant reduction in AHI between baseline and post-weight loss (SUBJECT, $F=11.11$, $p=0.007$) (Table 2). Furthermore, there was an interaction effect of SUBJECT*GROUP ($F=9.00$, $p=0.005$) (Figure 2). Baseline weight, the change in weight (between baseline and after weight loss), and the percent change in weight (from baseline) were mildly correlated with the change in AHI. These variables were considered as covariates on this basis. In the case of each of these variables, when it was added to the 2-way ANOVA model, there was not a unique effect of weight on the change in AHI. Absolute changes in AHI between baseline and post-weight loss within the OSA groups (normal, mild, and moderate AHI) are shown in Table 2. A post-hoc analysis (Tukey HSD) revealed a significant difference between the normal and moderate OSA groups only ($p=0.009$), and the mild and moderate groups ($p=0.006$) (Figure 2). Changes in AHI by stage of sleep (REM vs. non-REM) and sleep position (supine vs. non-supine) were also assessed (Table 2). However, some participants did not sleep in both supine and non-supine positions and data were not available. Similarly, data for AHI by REM and non-REM sleep are available for $n=12$. No significant differences were detected.

Sleep Data—Table 3 shows changes in sleep parameters as measured in the sleep studies. There was a significant reduction in wakefulness after sleep onset ($F=7.49$; $p=0.019$). Sleep efficiency improved after weight loss, but just missed the cutoff for significance ($F=6.34$; $p=0.026$). The percent of time in stage 1 sleep was significantly reduced in the 2-way ANOVA model ($F=8.38$; $p=0.015$ for SUBJECT; $F=16.225$; $p=0.01$ for GROUP). The post-hoc analysis (Tukey HSD) showed that the normal and mild OSA groups were different in terms of the percent of time in Stage 1 sleep ($p<0.0001$), and the normal and moderate OSA groups were different ($p=0.023$). Arousals (arousal index (ARI)) occurred more frequently

during the post-weight loss study ($F=18.13$, $p=0.001$). There was a significant improvement in both minimum oxygen saturation (minSaO_2) ($F=7.59$, $p=0.016$) (Figure 3a) and mean SaO_2 during sleep ($F=6.89$, $p=0.022$) (Figure 3b). There were no changes in total sleep time or time in bed. Similarly, data for wakefulness during sleep (WASO) are available for $n=12$. Consistent with the change in AHI, the hypopnea index (HI) was also significantly reduced between baseline and post-weight loss ($F=7.80$; $p=0.018$ for SUBJECT; $F=6.07$; $p=0.017$ for GROUP). The post-hoc analysis (Tukey HSD) showed that the mild and moderate OSA groups were different ($p=0.017$) in terms of HI.

Neck Morphology Data—A reduction in the right lateral subcutaneous fat width occurred with weight loss ($F=39.024$; $p<0.0001$). No other significant changes in anatomical structures were seen. The tongue area was also reduced, but missed the level of significance ($F=5.95$, $p=0.03$).

Oxygen Consumption and Carbon Dioxide Production—Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) were measured continuously during the 16-hour stay in the whole-room calorimeter, and are presented as mean values over the sleep period. As shown in Figure 3c, VO_2 decreased from 0.285 ± 0.012 L/min during the baseline sleep study to 0.234 ± 0.016 L/min during the post-weight loss study ($F=24.85$, $p<0.0001$). Moreover, VCO_2 decreased from 0.231 ± 0.009 L/min to 0.186 ± 0.012 L/min ($F=27.74$, $p<0.0001$) (Figure 3d).

Pulmonary function tests—The FVC increased significantly between baseline and post-weight loss (3.6 ± 0.21 to 3.9 ± 0.23 L, $F=9.80$, $p=0.008$), as did the FEV_1 (2.8 ± 0.15 to 3.1 ± 0.19 L, $F=9.61$, $p=0.008$), and the $\text{FEF}_{25\%-75\%}$ (2.6 ± 0.23 to 2.9 ± 0.26 , $F=9.25$, $p=0.009$).

Perceived Sleep Quality—In this study, Cronbach's α was 0.73, and inter-item correlations between 6 component scores and the global PSQI score ranged from 0.457–0.849. There were no significant changes in perceived sleep quality over time as weight was lost and maintained (absolute global scores at baseline, 8.67 ± 1.12 ; after weight loss, 8.167 ± 1.22 ; after weight maintenance, 7.92 ± 1.47 ; $F=0.303$; $p>0.05$). Additionally, there were no correlations between the severity of OSA and perceived sleep quality. Of note, the global scores in this study population fall between population norms established for Disorder of Initiating and Maintaining Sleep (reported mean global score = 10.38 ± 4.57) and Disorders of Excessive Somnolence (reported mean global score = 6.53 ± 2.98) (25).

DISCUSSION

The main outcome of this study was the change in apnea/hypopnea index (AHI) from before to after weight loss. The goals of this study were to determine if weight loss altered pharyngeal patency, oxygen consumption (VO_2) and carbon dioxide production (VCO_2) during sleep, and sleep quality in severely obese adults. We found that although our subjects remained severely obese after weight loss, there was an overall significant decrease in AHI in this group of patients. Importantly, this decrease was dependent on the severity of OSA such that those with more severe OSA had a greater improvement in AHI. There were also significant decrements in mean VO_2 and VCO_2 during sleep after weight loss, as well as improvements in pulmonary function. While pharyngeal patency did not improve symmetrically, minSaO_2 and mean SaO_2 during sleep were improved after weight loss. The sleep studies further revealed that arousals became more frequent. Finally, these patients did not perceive a significant improvement in overall sleep quality with weight loss.

There are numerous reports of weight reduction interventions in obese patients with OSA. Some studies have assessed the benefit of bariatric surgery (27,28), while others have investigated diet-induced weight loss (26,29,29,30). Whatever the method of weight reduction, these studies typically demonstrated that at least some people have acute reductions in SDB and improved sleep quality, although some have suggested that such benefits are not always long-term (27,30). Peppard and colleagues (31), in particular, demonstrated in a large population-based, prospective cohort study ($n=690$) that a dose-response relationship existed between weight and AHI. Specifically, as BMI increased, AHI also increased independent of baseline AHI. Our data contribute further by showing that people with worse OSA, as reflected by AHI, stand to benefit more substantially from even moderate weight loss in improving their SDB status. While we did not demonstrate the same type of dose-response relationship as in the study of Peppard et al. (31), our mechanistic study was carried out in a far-smaller cohort ($n=14$ vs. $n=690$) that was mainly comprised of females ($n=11$ in our study, compared to $>50\%$ males in the larger study), the participants were substantially more obese ((mean $\pm$ SD) baseline BMI = 48 ± 11 kg/m² in current study vs. 29 ± 6 kg/m² in the larger study), and our subjects were excluded for having a previously established diagnosis of OSA or severe OSA (AHI >30). Since OSA has approximately twice the prevalence in middle-aged obese men compared to their female counterparts (3,13,32), it could be that the gender imbalance in our cohort precluded the discovery of a dose-response relationship. However, the participants in our cohort were severely obese, vs. overweight (BMI <30 kg/m²) (33), and our data send a strong message for the improvements that are possible in a setting of modest weight loss in terms of AHI.

Although attention has previously focused upon the role of obesity in promoting OSA and its subsequent impact upon sleep quality, recent reports suggest that obese subjects can suffer from sleep disturbance and EDS in the absence of discrete OSA (2,8). This was likely the case in this cohort of men and women, since none of them met pre-study criteria for treatment of OSA (AHI >30) via positive airway pressure. Vgontzas and associates (4) confirmed this when they compared sleep characteristics of 73 severely obese patients without OSA to 45 controls (mean BMI <25.0 kg/m²) matched for age. The obese patients demonstrated poorer sleep parameters as assessed by polysomnography, and 57% of the obese patients complained of moderately severe EDS compared to only 2% of controls. Daytime nap studies confirmed the presence of EDS in the obese patients. These observations pointed to the idea that obesity alone can be a significant contributor to sleep disruption and EDS. It was speculated that sleepiness resulted from the combination of sleep disruptive mechanical effects of excess weight, or a possible circadian and/or metabolic abnormality related to obesity. More recently, scientific discourse has been centered on the role insulin resistance (13,34,35), visceral obesity (36), and inflammation (37) may play in the development of OSA, and some investigators now question if OSA could be a determinant of obesity, instead of obesity leading to OSA (7).

Obesity also adds an elastic load to the chest wall, reducing chest wall and total respiratory system compliance while possibly interposing an inspiratory threshold load (38). The reduction in lung volume common in severe obesity can also increase small airway and lung tissue resistance (38). In the current study we did not detect significant changes in awake, upright static lung volumes after weight loss, although our patients remained severely obese after weight loss. However, there were significant and proportional increments in FEV₁ and FVC. It therefore seems possible that the observed improvement in pulmonary function measures may have resulted from a concurrent increase in pharyngeal patency and reduction in pharyngeal resistance, as suggested by Stauffer and colleagues (39), although we did not observe this full effect. There were also reductions in both VO₂ and VCO₂ during sleep from baseline to post-weight reduction studies. While this is at least partly due to the reduction in body weight with its associated reduction in basal metabolic rate and energy

expenditure (40), this could also reflect a weight loss-associated reduction in the work of breathing. Kress et al. demonstrated a much higher total VO_2 in awake, quietly breathing, severely obese patients in comparison to control patients (41). When these same subjects were re-evaluated after paralysis, intubation, and mechanical ventilation, the obese patients demonstrated a 16% reduction in VO_2 , while the controls demonstrated a reduction of <1%. Thus, it appeared that morbidly obese patients dedicated a high portion of total VO_2 to respiratory work even during quiet breathing. It seems likely that at least part of the reduction in VO_2 we observed during sleep after weight loss reflects an associated decrease in the work of breathing.

It was surprising to find that weight loss did not portend improvements in neck morphology in these severely obese patients. Given the previous observations of pharyngeal structure and function in obese OSA patients (1,42–44), it seems likely that severe obesity would be associated with an anatomically narrowed pharynx even in the absence of discrete OSA. Such narrowing would constitute a resistive load that might contribute to sleep disruption (9). Others have assessed the effects of weight loss on upper airway function/morphology in obese patients with OSA. Specifically, it has been shown that weight loss is associated with a reduction in parapharyngeal adipose tissue (42), improved pharyngeal function via a reduction in lung volume dependence of pharyngeal cross-sectional area (43), and reduced upper airway collapsibility in response to negative pressure (44). Schwab et al. (21) suggested that lateral pharyngeal wall muscle thickness was a more important determinant of airway narrowing than the parapharyngeal fat pads, while Resta et al. (2) reported that neck circumference was a strong predictor of the severity of OSA. Unfortunately, our measurements concentrated on soft tissue anatomy. More recently, it was reported that in a sample of 138 men and women, properties of the upper airway structure correlated with the severity of SDB in men only, and that in general, women tended to exhibit more favorable airway function when compared to men (45). If this is the case, then our data describing the changes in neck morphology are limited since our sample was predominantly comprised of women. Alternatively, it is possible that we did not see significant changes simply due to the small sample size that was necessitated by the intense nature of this investigation.

Overall, perceived sleep quality did not change significantly in these patients, although there was a significant decrease in WASO, a non-significant (but possibly clinically significant) increase in sleep efficiency, and a remarkable increase in arousal frequency by polysomnography. This latter observation initially appeared to contradict our hypothesis; specifically, that weight loss promotes improved sleep quality in severely obese patients. One potential explanation could be that over the previous 3–6 months of maintained weight loss, sleep efficiency was consistently improved in comparison to pre-weight loss sleep. Since it has been demonstrated that sleep deprivation blunts arousal responses to a variety of stimuli (46,47), it may be that in the relatively sleep-deprived baseline state, patients experienced fewer arousals in response to the confined environment and instrumentation, while after weight loss and in a more sleep-replete state, the stimuli of the environment and instrumentation were more likely to trigger arousal. Therefore, it is possible that these patients did not perceive improved sleep quality as assessed by the PSQI because they experienced more frequent arousals. This explanation remains speculative.

There are several potential limitations to our study that warrant discussion. First, epidemiologic data support that more men have OSA, and this study was mostly comprised of females. It is possible that if more men had been enrolled in the study, changes in neck morphology would have been more apparent. However, there was one male participant in each AHI group, and thus they did not dominate one particular group. It is also a potential limitation that the sample size in this investigation was small. We acknowledge that the sleep data recorded even after acclimatization are likely not representative of a normal night

at home, given that the patients were confined to a small, physically isolated chamber while instrumented with a variety of recording devices, including many electrodes in triplicate. Moreover, the sleep technicians were not blinded to treatment (pre- vs. post-weight loss). It is also a limitation that, at the time this study was conducted, thermocouples were used to measure hypopneas instead of the now widely accepted method of using nasal pressure transducers. The axial and sagittal MRI scans were each performed over approximately 3 minutes of awake breathing, and our images may therefore not be fully representative of the same structures during sleep. However, subjects were instrumented identically during every study, whether conducted for acclimatization or actual data recording. For the MRI technique, the protocol of Schwab et al. (21) was strictly followed to avoid user prejudice in the determination of which slices to analyze and the choice of regions for area measures. The axial images with the smallest airways were analyzed, but we acknowledge that changes in airway area could reflect not only a true change in airway caliber, but also even a slight difference in head tilt during different scans. Every effort was made to standardize positioning, and the same technician performed all scans.

In conclusion, we have confirmed in this mechanistic, carefully executed study that these severely obese patients demonstrated an improved AHI after even modest weight loss. Moreover, we have demonstrated that those with more severe OSA as reflected by AHI showed a greater reduction in SDB. After weight loss, this entire group of subjects demonstrated improved nocturnal oxygen saturation and a reduced total work during sleep, as manifested by reductions in total VO_2 and VCO_2 . Such changes could reflect the overall reduction in body mass. We believe these data support a strong message of prevention, since modest weight loss in the severely obese may prevent or attenuate the serious complication of OSA and its associated impairments.

Acknowledgments

This study was funded by a grant from the Slim Fast® Foods Company Medical Department, and by a grant from the National Institutes of Health, Division of Research Resources, Colorado Clinical and Translational Sciences Institute, grant #RR-00051. We greatly acknowledge the expertise of Therese Ida, MS, RD, Jere Hamilton, BS, Ken Rothwell, RPSGT and Daniel Locke RPSGT, and the laboratory and nursing staff on the CTSC at UCD.

Reference List

1. Sloan EP, Shapiro CM. Obstructive sleep apnea in a consecutive series of obese women. *Int J Eat Disord.* 1995; 17(2):167–73. [PubMed: 7757098]
2. Resta O, Foschino-Barbaro MP, Legari G, et al. Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. *Int J Obes Relat Metab Disord.* 2001; 25(5):669–75. [PubMed: 11360149]
3. Vgontzas AN, Kales A. Sleep and its disorders. *Annu Rev Med.* 1999; 50:387–400. [PubMed: 10073285]
4. Vgontzas AN, Bixler EO, Tan TL, Kantner D, Martin LF, Kales A. Obesity without sleep apnea is associated with daytime sleepiness. *Arch Intern Med.* 1998; 158(12):1333–7. [PubMed: 9645828]
5. Strollo PJ Jr, Rogers RM. Obstructive sleep apnea. *N Engl J Med.* 1996; 334(2):99–104. [PubMed: 8531966]
6. Strohl KP, Bonnie RJ, Findley L, et al. Sleep apnea, sleepiness and driving risk. *Am J Respir Crit Care Med.* 1994; 150:1463–73. [PubMed: 7952578]
7. Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences. *Nutr Metab Cardiovasc Dis.* 2007; 17(3):233–40. [PubMed: 17314035]
8. van Kralingen KW, de Kanter W, de Groot GH, et al. Assessment of sleep complaints and sleep-disordered breathing in a consecutive series of obese patients. *Respiration.* 1999; 66(4):312–6. [PubMed: 10523171]

9. Guilleminault C, Stoohs R, Clerk A, Cetel M, Maistros P. A cause of excessive daytime sleepiness. The upper airway resistance syndrome. *Chest*. 1993; 104(3):781–7. [PubMed: 8365289]
10. Zerah F, Harf A, Perlemuter L, Lorino H, Lorino AM, Atlan G. Effects of obesity on respiratory resistance. *Chest*. 1993; 103(5):1470–6. [PubMed: 8486029]
11. Sharp JT, Henry JP, Sweaney SK. The total work of breathing in normal and obese men. *J Clin Invest*. 1964; 43(728):739.
12. Rochester, DF. Obesity and pulmonary function. In: Alpeut, MA.; Alexander, JK., editors. *The heart and lung in obesity*. New York, N.Y: Future Publishing Company; 1998. p. 108-132.
13. Vgontzas AN, Bixler EO, Chrousos GP. Metabolic disturbances in obesity versus sleep apnoea: the importance of visceral obesity and insulin resistance. *J Intern Med*. 2003; 254(1):32–44. [PubMed: 12823641]
14. Poirier P, Hernandez TL, Weil KM, Shepard TJ, Eckel RH. Impact of diet-induced weight loss on the cardiac autonomic nervous system in severe obesity. *Obes Res*. 2003; 11(9):1040–7. [PubMed: 12972673]
15. Toussaint M, Luthringer R, Schaltenbrand N, et al. First-night effect in normal subjects and psychiatric inpatients. *Sleep*. 1995; 18(6):463–9. [PubMed: 7481418]
16. Shepard TY, Weil KM, Sharp TA, et al. Occasional physical inactivity combined with a high-fat diet may be important in the development and maintenance of obesity in human subjects. *Am J Clin Nutr*. 2001; 73(4):703–8. [PubMed: 11273843]
17. Desbuquois B, Aurbach GD. Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. *J Clin Endocrinol Metab*. 1971; 33(5):732–8. [PubMed: 5166455]
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972; 18(6):499–502. [PubMed: 4337382]
19. Rechtschaffen, A.; Kales, A. US Public Health Service: Manual of standardized terminology, techniques and scoring system for sleep stage of human subjects. Washington, D.C: U.S. Government Printing Office; 1968.
20. The Report of an American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. *Sleep*. 1999; 22(5):667–89. [PubMed: 10450601]
21. 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; 152:1673–89. [PubMed: 7582313]
22. Crapo RO, Morris AH, Gardner RM. Reference spirometric values using techniques and equipment that meet ATS recommendations. *Am Rev Respir Dis*. 1981; 123:659–64. [PubMed: 7271065]
23. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir*. 1982; 18:419–25. [PubMed: 7074238]
24. Buysse DJ, Reynolds CF III, Monk TH, Hoch CC, Yeager AL, Kupfer DJ. Quantification of subjective sleep quality in healthy elderly men and women using the Pittsburgh Sleep Quality Index (PSQI). *Sleep*. 1991; 14(4):331–8. [PubMed: 1947597]
25. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res*. 1989; 28(2):193–213. [PubMed: 2748771]
26. 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; 103:850–5. [PubMed: 3933396]
27. 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–6S. [PubMed: 1733135]
28. Sugerman HJ, Fairman RP, Sood RK, Engle K, Wolfe L, Kellum JM. Long-term effects of gastric surgery for treating respiratory insufficiency of obesity. *Am J Clin Nutr*. 1992; 55:597S–601S. [PubMed: 1733136]

29. 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; 92:631–7. [PubMed: 3652748]
30. Sampol G, Munoz X, Sagales MT, et al. Long-term efficacy of dietary weight loss in sleep apnoea/hypopnoea syndrome. *Eur Respir J*. 1998; 12(5):1156–9. [PubMed: 9864013]
31. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000; 284(23):3015–21. [PubMed: 11122588]
32. 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(17):1230–5. [PubMed: 8464434]
33. National Heart Lung and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults: The Evidence Report. National Institutes of Health; 1998. p. 98-4083.
34. Tassone F, Lanfranco F, Gianotti L, et al. Obstructive sleep apnoea syndrome impairs insulin sensitivity independently of anthropometric variables. *Clin Endocrinol (Oxf)*. 2003; 59(3):374–9. [PubMed: 12919162]
35. Ip MS, Lam B, Ng MM, Lam WK, Tsang KW, Lam KS. Obstructive sleep apnea is independently associated with insulin resistance. *Am J Respir Crit Care Med*. 2002; 165(5):670–6. [PubMed: 11874812]
36. Shinohara E, Kihara S, Yamashita S, et al. Visceral fat accumulation as an important risk factor for obstructive sleep apnoea syndrome in obese subjects. *J Intern Med*. 1997; 241(1):11–8. [PubMed: 9042088]
37. Peled N, Kassirer M, Shitrit D, et al. The association of OSA with insulin resistance, inflammation and metabolic syndrome. *Respir Med*. 2007; 101(8):1696–701. [PubMed: 17466499]
38. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci*. 2001; 321(4):249–79. [PubMed: 11307867]
39. Stauffer JL, White DP, Zwillich CW. Pulmonary function in obstructive sleep apnea. Relationships to pharyngeal resistance and cross-sectional area. *Chest*. 1990; 97(2):302–7. [PubMed: 2298054]
40. Wadden TA, Foster GD, Letizia KA, Mullen JL. Long-term effects of dieting on resting metabolic rate in obese outpatients. *JAMA*. 1990; 264(6):707–11. [PubMed: 2374273]
41. Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing (VO(2)RESP) at rest. *Am J Respir Crit Care Med*. 1999; 160(3):883–6. [PubMed: 10471613]
42. Shelton KE, Woodson H, Gay S, Suratt PM. Pharyngeal fat in obstructive sleep apnea. *Am Rev Respir Dis*. 1993; 148(2):462–6. [PubMed: 8342912]
43. Rubenstein I, Colapinto N, Rotstein LE, Brown IG, Hoffstein V. Improvement in upper airway function after weight loss in patients with obstructive sleep apnea. *Am Rev Respir Dis*. 1988; 138:1192–5. [PubMed: 3202479]
44. Schwartz AR, Gold AR, Schubert N, et al. Effect of weight loss on upper airway collapsibility in obstructive sleep apnea. *Am Rev Respir Dis*. 1991; 144(3 Pt 1):494–8. [PubMed: 1892285]
45. Mohsenin V. Gender differences in the expression of sleep-disordered breathing : role of upper airway dimensions. *Chest*. 2001; 120(5):1442–7. [PubMed: 11713117]
46. Bowes G, Woolf GM, Sullivan CE, Phillipson EA. Effect of sleep fragmentation on ventilatory and arousal responses of sleeping dogs to respiratory stimuli. *Am Rev Respir Dis*. 1980; 122:899–908. [PubMed: 6779683]
47. Ballard RD, Tan WC, Kelly PL, Pak J, Pandey R, Martin RJ. Effect of sleep and sleep deprivation on ventilatory response to bronchoconstriction. *J Appl Physiol*. 1990; 69(2):490–7. [PubMed: 2228858]

Figure 1.

Change in weight (baseline vs. post-weight loss) for 14 patients completing the protocol during 9 months of study. Time points are in weeks, with week 26 as the start of diet phase 1 (DP1), 28 as a whole-room indirect calorimeter stay, 34 as the start of diet phase 2 (DP2), and 36 as a whole-room indirect calorimeter stay.

Figure 2.

Change in AHI between baseline and post-weight loss. The severity of OSA was a moderating variable to the reduction in AHI. Patients with more severe OSA showed a greater improvement in AHI compared to the groups with less severe or no OSA.

Figure 3.

Figure 3a, 3b, 3c, 3d. Changes (baseline vs. post-weight loss) in oxygen utilization and overall oxygen status during sleep. Figure 3a and 3b, respectively, show the increase in minimum oxygen saturation ($p=0.016$) and in oxygen saturation ($p=0.022$) from baseline (open bars) to post-weight reduction (filled bars) during sleep. Figures 3c and 3d, respectively, show the decreases in oxygen consumption (VO₂) ($p<0.0001$) and carbon dioxide production (VCO₂) ($p<0.0001$) as measured by indirect calorimetry.

Table 1

Baseline characteristics of 14 severely obese patients. Data are mean $\pm$ SD.

Variable	Value
Gender (M/F)	3/11
Age, years	43 $\pm$ 10
Weight, kg	134 $\pm$ 25
BMI, kg/m ²	48 $\pm$ 11
SBP, mm/Hg	132 $\pm$ 12
DBP, mm/Hg	74 $\pm$ 11
NPRQ	0.85 $\pm$ 0.3
BMR, kcal/day/kg	1.45 $\pm$ 0.32
Glucose, mg/dL	100 $\pm$ 14
Insulin, uU/mL	22 $\pm$ 12
Total Cholesterol, mg/dL	202 $\pm$ 57
LDL cholesterol, mg/dL	117 $\pm$ 47
HDL cholesterol, mg/dL	52 $\pm$ 16
Triglycerides, mg/dL	168 $\pm$ 62

SBP =systolic blood pressure; DBP =diastolic blood pressure; NPRQ =non-protein respiratory quotient; BMR =basal metabolic rate

Table 2

Absolute values for changes in apnea/hypopnea index, broken down by OSA group, REM and non-REM sleep, and sleep position.

	Baseline	Post-Weight Loss
AHI (<i>n</i> =14)	10.6±2.3	5.7±1.8 [‡]
- <i>Normal</i> (<i>n</i> =4)	2.3±1.3	2.7±1.1
- <i>Mild</i> (<i>n</i> =7)	9.4±1.1	8.6±3.2
- <i>Moderate</i> (<i>n</i> =3)	24.3±3.9	2.9±2.0
- REM sleep (<i>n</i> =12)	31±6	19±5
- Non-REM sleep (<i>n</i> =12)	8±2	4±1
- Supine (<i>n</i> =8)	18±7	5±2
- Non-supine (<i>n</i> =12)	11±2	7±2

AHI =apnea/hypopnea index, events per hour of sleep

[‡]*p*<0.025 for 2-way ANOVA model by SUBJECT and GROUP

Table 3

Absolute values for changes in sleep characteristics between baseline and after weight loss for 14 patients completing the protocol.

	Baseline	Post-Weight Loss
TST (min)	280±24.6	313.4±18.0
WASO (min)	77±15	53±16 ^{\$}
TIB (min)	428.5±14.6	391.6±14.2
Sleep Efficiency, %	66.4±6.1	81.1±4.6
Stage 1 (%)	22.2±4.4	17.7±3.1 [‡]
Stage 2 (%)	58.9±4.8	58.3±4.5
Stage 3–4 (%)	3.6±1.9	7.7±4.7
Stage REM (%)	15.5±2.3	16.4±2.5
ARI (arousals/hr)	8.06±1.4	17.1±3.0 ^{\$}
AWI (awakenings/hr)	4.0±1.0	4.77±1.3
MinSaO₂ (%)	83.4±1.9	89.1±1.2 ^{\$}
Mean SaO₂ (%)	90.4±1.1	94.1±1.0 ^{\$}
AI (apneas/hr)	1.14±0.4	0.4±0.1
HI (hypopneas/hr)	9.44±2.3	5.2±1.8 [‡]

^{\$} $p < 0.025$ for 1-way ANOVA model by SUBJECT

[‡] $p < 0.025$ for 2-way ANOVA model by SUBJECT and GROUP

TST =total sleep time; WASO =wakefulness after sleep onset; TIB =time in bed; ARI =arousal index; AWI =awakening index; SaO₂ =arterial oxygen saturation; AI =apnea index; HI =hypopnea index