Published in final edited form as:

Obes Surg. 2011 September ; 21(9): 1413–1423. doi:10.1007/s11695-011-0359-4.

Sleep Apnea Determines Soluble TNF- α Receptor 2 Response to Massive Weight Loss

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Parts of this study were presented at the Annual Congress of the European Respiratory Society, September 18–22, 2010, in Barcelona, Spain.

Conflict of Interest Statement The authors declare that they have no conflict of interest.

Abstract

Background—The effects of surgical weight loss (WL) on inflammatory biomarkers associated with sleep apnea remain unknown. We sought to determine if any bio-markers can predict amelioration of sleep apnea achieved by bariatric surgery. We hypothesized that surgical WL would substantially reduce severity of sleep apnea and levels of proinflammatory cytokines.

Methods—Twenty-three morbidly obese adults underwent anthropometric measurements, polysomnography, and serum biomarker profiling prior to and 1 year following bariatric surgery. We examined the effect of WL and amelioration of sleep apnea on metabolic and inflammatory markers.

Results—Surgical WL resulted in significant decreases in BMI (16.7 ± 5.97 kg/m²/median 365 days), apnea–hypopnea index (AHI), CRP, IL-6, sTNF α R1, sTNF α R2, and leptin levels, while ghrelin, adiponectin, and soluble leptin receptor concentrations increased significantly. Utilizing an AHI cutoff of 15 events/h, we found significantly elevated levels of baseline sTNF α R2 and greater post-WL sTNF α R2 decreases in subjects with baseline AHI ≥ 15 events/h compared to those with AHI < 15 events/h despite no significant differences in baseline BMI, age, and BMI. In a multivariable linear regression model adjusting for sex, age, impaired glucose metabolism, BMI, and follow-up period, the post-WL decreases in AHI were an independent predictor of the decreases in sTNF α R2 and altogether accounted for 46% of the variance of sTNF α R2 ($P=0.011$) in the entire cohort.

Conclusions—Of all the biomarkers, the decrease in sTNF α R2 was independently determined by the amelioration of sleep apnea achieved by bariatric surgery. The results suggest that sTNF α R2 may be a specific sleep apnea biomarker across a wide range of body weight.

Keywords

Bariatric surgery; Obesity; Sleep apnea; Soluble tumor necrosis factor- α receptor 2; Weight loss

Introduction

Sleep apnea is a prevalent and underdiagnosed sleep-related breathing disorder. It is characterized by recurrent episodes of upper airway collapse and obstruction during sleep due to defects in pharyngeal structure and neuromuscular control [1]. Sleep apnea is associated with substantial morbidity and mortality whose prevalence is linked to the current epidemic of obesity in many Western societies. Although obesity is an important risk factor for the development and progression of sleep apnea, the precise mechanisms linking the two disorders remain largely unknown.

An increasing body of evidence suggests that both obesity and sleep apnea have been associated with low-grade systemic inflammation [2], and that tumor necrosis factor- α (TNF- α) and high sensitive interleukin-6 (IL-6) may play an important role in this inflammatory response. Notwithstanding, previous studies investigating associations between sleep apnea and proinflammatory cytokines have demonstrated either positive or no associations between sleep apnea and either TNF- α [3–6] or IL-6 [4–6]. The impact of

sleep apnea on biomarkers also remains unclear in view of evidence demonstrating no change [7, 8] or reductions [9, 10] in inflammatory markers and blood cytokines by treatment with continuous positive airway pressure in these subjects with sleep apnea across a spectrum of obesity. Similarly, several studies have shown that bariatric surgery resulted in marked weight loss (WL) and improvements in sleep apnea and inflammation [11, 12]. However, the effect of amelioration of sleep apnea, achieved by bariatric surgery, on inflammatory markers (TNF- α , IL-6) in severe obesity remains to be unraveled. Furthermore, the impact of sleep apnea on TNF- α receptors and their soluble forms has not yet been sufficiently studied. To date, no study has assessed the levels of soluble TNF- α receptor 2 (sTNFR2) in sleep apnea patients while controlling for the degree of obesity and other potential covariates. Therefore, the inflammatory consequences of sleep apnea in severe obesity remain largely undefined.

The major goal of this study was to examine effects of surgical WL on obesity, sleep, sleep apnea, and selected biomarkers in morbidly obese adults, and to determine if any biomarkers can predict the resolution or amelioration of sleep apnea achieved by bariatric surgery. We hypothesized that surgical WL would substantially reduce the severity of sleep apnea and the levels of proinflammatory cytokines. To address these objectives, we recruited a group of morbidly obese subjects selected for bariatric surgery for the study since the massive WL that ensues offers a unique opportunity to examine biomarker responses related to improvements in sleep apnea in obesity.

Subjects and Methods

Study Design and Setting

This was a longitudinal study conducted in 2003–2009 in the Johns Hopkins Sleep Disorders Center and the Clinical Research Unit at Johns Hopkins Bayview Medical Center. The protocols were approved by the Western Institutional Review Board. The research was conducted in accordance with the ethical standards of the institutional and national committee on human experimentation. Written informed consent was obtained from all subjects before participating in the study.

Study Population

Participants recruited from the Johns Hopkins Center for Bariatric Surgery referred to our sleep center for evaluation of sleep-disordered breathing prior to and approximately 1 year after bariatric surgery were included.

Inclusion criteria were age ≥ 21 years and a body mass index (BMI; defined as weight in kilograms divided by the square of the height in meters) ≥ 35 kg/m². Exclusion criteria included pregnancy, acute or chronic infectious diseases, unstable cardiovascular disease, intrinsic lung disease, renal failure on dialysis, cirrhosis, bleeding disorders, sleep disorders other than sleep apnea, and supplemental oxygen use.

Twenty-three adults (14 women, nine men; 15 Caucasian, eight African American; aged 41.9 ± 8.6 years at baseline) who completed preoperative and postoperative evaluation were

enrolled. Roux-en-Y gastric bypass was performed in 21 study participants. One subject underwent a gastric sleeve resection and one biliopancreatic diversion with duodenal switch.

Study Procedures

Anthropometrics—Standard methods were employed to measure weight, height, sagittal abdominal diameter, and neck-, waist-, and hip circumferences, and to calculate BMI and waist-to-hip ratio (WHR). Obesity was considered mild if the BMI was 27–30 kg/m², moderate if 30–35 kg/m², severe if 35–40 kg/m², morbid (extreme/clinically severe) if 40–50 kg/m², super obesity if 50–60 kg/m², and super, super obesity if >60 kg/m² [13].

Polysomnography—Full-night polysomnography was performed using standard methodology. All physiologic signals were digitally acquired by Somnologica software (Somnologica Studio, Medcare Flaga, Reykjavik, Iceland). Each polysomnographic recording was visually scored in 30-s epochs according to standard criteria [14]. Respiratory events and arousals were scored according to established criteria [14–16]. The number of apneas and hypopneas per hour of sleep were calculated to obtain the apnea–hypopnea index (AHI). Sleep apnea was diagnosed using the criteria of the American Academy of Sleep Medicine [15]. Sleep apnea was considered mild if the AHI was 5–15 events/h, moderate if 15–30 events/h, and severe if ≥30 events/h [15].

Analytical Assay—A fasting blood sample was drawn on the morning after completion of each sleep study and assayed for selected biomarkers. Serum was stored at –80°C until assay. All samples and standards were run in duplicate and analyzed in the same batches.

Enzyme-linked immunosorbent assay was used for measurements of serum interleukin-1β (IL-1β), IL-6, interleukin-8 (IL-8), TNF-α, soluble TNF-α receptor 1 (sTNFαR1), sTNFαR2 (MSD, Gaithersburg, MD), serum leptin, and soluble leptin receptor (R&D Systems, Inc., Minneapolis, MN), serum adiponectin (Millipore, Inc., St. Charles, MO), serum C-reactive protein (CRP; R&D Systems, Inc., Minneapolis, MN), and for measurements of baseline serum insulin (Millipore Corp., Billerica, MA). Serum concentrations of ghrelin were determined by radioimmunoassay using commercial kits from Millipore, Inc. (St. Charles, MO).

Intra-assay coefficients of variation (CV) were 7.79% for IL-1β, 7.79% for IL-6, 4.41% for IL-8, 7.71% for TNF-α, 1.31% for sTNFαR1, 2.55% for sTNFαR2, 8.08% for leptin, 3.1% for soluble leptin receptor, 2.11% for adiponectin, and 5.17% for ghrelin. Inter-assay CVs were 5.96% for IL-1β, 5.96% for IL-6, 14.92% for IL-8, 11.76% for TNF-α, 12.64% for sTNFαR1, 6.45% for sTNFαR2, 3.87% for leptin, 7.7% for soluble leptin receptor, 1.65% for adiponectin, and 6.69% for ghrelin. The minimum detectable concentrations were 0.18 pg/mL for IL-1β, 0.039 pg/mL for IL-6, 0.14 pg/mL for IL-8, 0.48 pg/mL for TNF-α, 0.77 pg/mL for sTNFαR1, 0.6 pg/mL for sTNFαR2, 0.47 ng/mL for leptin, 0.057 ng/mL for soluble leptin receptor, 1.5 ng/mL for adiponectin, and 10 pg/mL for ghrelin.

Statistical Analyses

The Shapiro–Wilk test was applied to test for a normal distribution. Continuous variables with normal distribution are presented as means±standard deviation (SD) and compared with use of a Student's *t* test. Continuous variables with non-normal distributions are presented as medians and interquartile ranges (IQR) and compared with use of the Wilcoxon-matched pairs signed-ranks test or the Wilcoxon rank-sum test. The chi-square test was applied to examine patterns between categorical variables.

The Pearson product–moment correlation coefficient (*r*), Spearman's rank correlation coefficient, and multiple regression analyses were utilized to examine relationships among the variables. We performed multivariate linear regression analyses to determine whether unadjusted associations between post-weight loss changes in sleep apnea severity and inflammatory markers persisted after controlling for potential confounders. Potential confounding variables included in all multivariate models as covariates were sex, age, impaired glucose metabolism, absolute post-WL change in BMI, and follow-up period. We performed sensitivity analyses using absolute post-WL changes in waist circumference as a covariate instead of absolute post-WL change in BMI in the multivariate models. The only independent predictor was the absolute post-WL change in AHI. The dependent variables were absolute post-WL changes in levels of biomarkers, derived from the pre-and post-WL blood test evaluation. Coefficients of partial determination were calculated to explore the relative effects of each of the selected variable on an outcome measure in the model. For each of the independent variables/covariates included in the regression models, we checked for the presence of multicollinearity by calculating variance inflation factors and tolerances. If the reciprocal of the variance inflation factor was smaller than the predetermined tolerance, the associated predictor variable was removed from the regression model.

To achieve approximate normality, the AHI values were log-transformed prior to analysis according to the formula $\log(\text{AHI}+1)$. The back-transformed values are reported for ease of interpretation. Absolute changes () in AHI, BMI, and biomarkers were calculated by subtracting pre-WL values from post-WL values.

Findings were considered to be statistically significant at the 5% level. All statistical calculations were performed using Stata 11.0 (StataCorp LP, College Station, TX).

Results

Baseline Sample Characteristics

At baseline, the subjects were hyperinsulinemic (insulin 15.4 ± 7.38 mU/l) and had excess amounts of centrally localized, abdominal fat as indicated by waist circumference, WHR, and other anthropometric measures. Fifty-two percent of the participants had normal glucose metabolism, 26% had prediabetes and 22% type 2 diabetes [17]. According to the results of baseline polysomnography, 96% of the participants met accepted criteria for sleep apnea. Moreover, 52% of the subjects had severe sleep apnea at baseline with a predominance of hypopneic events.

The average time interval between the bariatric surgery and postoperative evaluation was 417 ± 176 days (median 365 days). Table 1 shows participants' clinical characteristics before and following WL.

Effects of Bariatric Surgery

Obesity and Regional Adiposity—The average WL 50.8 ± 18.93 kg/median 365 days was associated with significant decreases in BMI (16.7 ± 5.97 kg/m²); neck-, waist-, and hip circumference; WHR; and sagittal abdominal diameter (Table 1). Using BMI cutoffs for obesity categories, the severity of obesity improved in 96% of subjects. There was greater WL in subjects who were more obese at baseline. Figure 1 shows post-WL changes in BMI for the three tertiles of baseline BMI. Despite the massive WL, 48% of the participants continued to have BMI >35 kg/m² after 1 year.

Sleep Apnea and Sleep Architecture—Using AHI cutoffs for mild, moderate, and severe disease, the severity of sleep apnea improved in 91% of the participants (Table 1). Despite substantial decreases in AHI, 48% of the subjects (77.8% of men and 28.6% of women) had persistent sleep apnea (AHI >5 events/h) at follow-up. In addition to dramatic post-WL improvements in AHI and nocturnal oxyhemoglobin saturation parameters, distinct alterations in sleep architecture were observed. The percent of the total sleep time spent in stage 3 of non-rapid eye movement (NREM) sleep (N3) was significantly reduced, while the rapid eye movement (REM) sleep percentage increased significantly (Table 1). The increase in REM sleep percentage was predicted by male sex and by decreases in leptin/leptin receptor ratio even after adjustment for AHI, BMI, and age ($P=0.025$). The leptin/leptin receptor ratio explained 32.6% ($P=0.011$) and sex 26.7% ($P=0.024$) of the variance of the post-WL change in REM sleep percentage when the other variables were included in the model.

Inflammatory Markers and Adipokines—Surgical WL was associated with significant decreases in serum CRP, IL-6, sTNF α R1, sTNF α R2, leptin levels, and leptin/leptin receptor ratio, while ghrelin, adiponectin, soluble leptin receptor concentrations, and TNF- α /IL-6 ratio increased significantly (Table 1). There was a trend of post-WL increase in IL-8 levels and no significant changes in IL-1 β and TNF- α levels. From all of the inflammatory cytokines, the ratio of TNF- α to IL-6 was most closely inversely associated with CRP levels at baseline ($r=-0.68$; $P<0.001$). Figure 2 shows individual changes in selected inflammatory biomarkers following the WL.

Sex Differences—Table 2 presents sex differences in participants' characteristics. Compared to women, men had lower baseline leptin levels, higher TNF- α levels pre- and post-WL, higher total AHI pre- and post-WL, and greater AHI with WL. Although sleep apnea during NREM sleep was more severe in men, there was no significant difference in sleep apnea severity between the two sexes during REM sleep. Despite similarities in age and decreases in weight and central adiposity between men and women, women had greater decreases in leptin/leptin receptor ratio and CRP following the WL than men. In women unlike men, the BMI was an independent predictor of leptin/leptin receptor ratio even after adjustment for age and follow-up period ($P=0.003$).

Need for Medications—Surgical WL was associated with discontinuation of metformin in three study participants, glitazones in four, and sulfonylureas in two participants. Six subjects discontinued diuretics. The treatment with angiotensin-converting enzyme inhibitors was discontinued in three subjects. Two participants discontinued calcium channel blocker therapy. The use of statins was discontinued in two subjects. While antipsychotic treatment was discontinued in one subject, another three participants started on an antipsychotic medication within 1 year following the bariatric surgery.

Biomarker Response to Weight Loss in Sleep Apnea

Using univariate analysis, we compared baseline levels of biomarkers and biomarker responses to WL in the subjects stratified by baseline sleep apnea severity. Despite intensive efforts to include the non-apneic obese controls, there was only one non-apneic participant in the cohort of 23 morbidly obese participants at baseline, which precluded inclusion of the obese non-apneic control group. Therefore, utilizing the criteria of the American Academy of Sleep Medicine, we divided subjects into two subgroups: (1) the non-apneic subject and subjects with mild sleep apnea (AHI <15 events/h), and (2) subjects with moderate to severe sleep apnea (AHI ≥ 15 events/h). Utilizing the AHI cutoff of 15 events/h, we found significantly elevated levels of baseline sTNFαR2 and decreased TNF-α/IL-6 ratio in subjects with AHI ≥ 15 events/h, compared to those with AHI <15 events/h. Furthermore, the subjects with moderate to severe sleep apnea had greater post-WL decreases in sTNFαR2 and greater increases in TNF-α/IL-6 ratio than those with less severe sleep apnea (Fig. 3). There were no significant differences in baseline age, BMI, amount of WL (BMI, weight, waist circumference), and baseline or post-WL levels of other biomarkers between the two subgroups. Nevertheless, the individuals with AHI ≥ 15 events/h had a trend towards higher baseline IL-6 levels ($P=0.05$) and were more likely to be male ($P<0.001$) and to have prediabetes or diabetes ($P<0.001$).

Correlation analyses were utilized to identify variables associated with sleep apnea improvement and those associated with amount of WL. Table 3 displays the correlations in all study participants and in subgroups based on sex. Following WL, the AHI was positively correlated with sTNFαR2 and negatively with TNF-α/IL-6 ratio in all participants. In addition, both baseline and follow-up levels of sTNFαR2 were significantly positively correlated with baseline and follow-up AHI, respectively, in all study participants. Similar negative associations were observed between the sTNFαR2 and average low oxyhemoglobin saturation during sleep. The positive associations of AHI with IL-6 observed in the entire cohort were driven by strong correlations found only in subjects with prediabetes and diabetes ($r=0.69$; $P=0.019$). Figure 4 illustrates linear associations between post-WL changes in sleep apnea severity and changes in sTNFαR2 and TNF-α/IL-6 ratio in the entire cohort.

Multivariable analyses were conducted to determine whether unadjusted associations between sleep apnea severity and inflammatory markers persisted after controlling for potential confounders. In a multivariable linear regression model adjusting for sex, age, impaired glucose metabolism, BMI, and follow-up period, the AHI was an independent predictor of sTNFαR2 and altogether accounted for 46% of the variance of sTNFαR2

($P=0.011$) in the entire cohort following the WL. A similar independent linear prediction was observed for TNF- α /IL-6 ratio ($P=0.004$). Results were similar when BMI was replaced by waist circumference in the regression models.

Discussion

Our study demonstrated that in morbid obesity, untreated sleep apnea and its improvement with surgical WL determined baseline sTNFaR2 levels and sTNFaR2 bio-marker response to WL, which was independent of sex, age, impaired glucose metabolism, amount of WL, and the follow-up period. These findings offer further support for the recognized association between sleep apnea and chronic low-grade systemic inflammation. In the present study, we demonstrate that sleep apnea in morbid obesity is associated with two- to threefold elevated levels of baseline serum CRP and sTNFaR2 over the reference range. Moreover, as WL ensued, these inflammatory markers decreased significantly, and the decrease in sTNFaR2 was independently related to sleep apnea improvement. In contrast, WL was associated with significant changes in sleep architecture, which were not related to sleep apnea improvements.

TNFaR1 and TNFaR2 are genetically distinct receptors that mediate TNF- α 's proinflammatory signals [18]. Soluble TNF- α receptor forms are found in the serum and urine, and arise when extracellular domains of the receptors are shed into the circulation [19]. While only a few human studies have implicated sTNFaR1 as an important regulatory component in sleep regulation [10, 20], a role of the sTNFaR2 in sleep apnea remains unknown. Elevated levels of sTNFaR2 have been reported in obese individuals [21] and in obesity-associated diseases [22, 23]. Nevertheless, these studies have not examined associations between sTNFaR2 and sleep apnea while controlling for the degree of obesity and other potential covariates.

Several lines of evidence have emerged from our study to suggest that sTNFaR2 is a specific marker for sleep apnea activity in obesity. First, sTNFaR2 levels were significantly elevated at baseline in the subgroup with moderate to severe sleep apnea. Second, the decrease in sTNFaR2 levels strongly correlated with the fall in AHI at 1 year follow-up in both men and women and for the group as a whole. Third, multivariable models confirmed that changes in sTNFaR2 were associated with changes in sleep apnea severity even after accounting for potential covariates of the response to WL. Importantly, while levels of both sTNFaR1 and sTNFaR2 decreased significantly with WL, only decreases in sTNFaR2 were independently associated with sleep apnea improvements. These findings suggest that sTNFaR2 reflects sleep apnea disease severity even after massive WL, and that its decrease with WL is related to improvements in sleep apnea rather than to WL per se.

Further, although the absolute levels of TNF- α did not change at 1 year follow-up, the ratio of TNF- α to IL-6 was significantly increased and associated with amelioration of sleep apnea independently of sex, age, impaired glucose metabolism, and amount of WL. These findings suggest that TNF- α and IL-6 are dynamically interrelated within the individual, supporting dynamic interactions between these adipocytokines [24]. The results also partially support previous studies indicating that TNF- α stimulates the secretion of IL-6 via

an NF-kappaB-dependent pathway [25], and that both TNF- α receptors independently play a role in activating NF-kappaB [18]. Moreover, the close inverse associations of the TNF- α /IL-6 ratio with both CRP and sleep apnea severity observed in our study suggest that the ratio might be a marker for protection from chronic low-grade inflammation in sleep apnea and obesity.

While the dramatic WL was paralleled by reductions in IL-6 and CRP in our cohort, another NF-kappaB-dependent cytokine, IL-8, was unexpectedly elevated at 1 year follow-up. Bruun and coworkers [26] have reported similar findings in men undergoing bariatric surgery. Although the mechanism for increases in IL-8 following the surgical WL is unclear, postoperative tissue infection, ischemia, trauma, and inflammation are associated with an influx of neutrophils that can release IL-8 [27]. Besides its secretion from adipocytes, neutrophils, and other cell types involved in inflammatory responses, post-WL increases in IL-8 could also be due to differential regulation of IL-8 compared to IL-6 and TNF- α by WL [26].

Neurohumoral factors may influence WL responses during sleep. Several factors may account for the distinct alterations in sleep architecture following WL. The reduced time in N3 and increased time in REM sleep observed in our study agree with previous findings by Willi and coworkers [28] who reported significant increases in REM sleep and decreases in N3 in morbidly obese adolescents following WL. Here, we have demonstrated that the increases in REM sleep percentage were independently predicted by male sex and by post-WL decreases in leptin/leptin receptor ratio. This observation partially confirms findings by Sinton and coworkers [29] who showed that in normally fed rats, administration of leptin significantly decreased the duration of REM sleep and increased the duration of N3. In view of these findings, we speculate that changes in sleep architecture following WL might be mediated via leptin pathways or other neuroendocrine factors.

There are several limitations to our study that should be considered in relation to the findings. First, the relatively small sample size precluded more comprehensive modeling of observed associations between sleep apnea and adipocytokines in obesity. Second, the metabolic assessment was limited to a baseline testing of fasting glucose and insulin. Third, we did not assess energy expenditure and did not take this item into account in analysis of the biomarker changes following the WL. Fourth, the surgical WL was associated with reductions or the discontinuation of medications for comorbid conditions in some of the patients, which could have an unpredictable impact on biomarkers. However, we have performed additional multivariate regression analyses to determine whether any post-weight loss changes in medications were linked to the dependent outcome variable. The results showed that the changes in medications had no effect on post-weight loss biomarker levels. When the medications were added to the regression model as covariates, the AHI remained an independent predictor for changes in sTNF α R2 ($P<0.05$). Fifth, sex-related differences in sleep apnea severity could confound our assessments of biomarkers and their responses to WL. However, despite sex-related differences in sleep apnea severity, we found that WL trajectories in sTNF α R2 were similar in the men and women, and were dependent on the presence of sleep apnea at baseline and on its improvement with WL, suggesting that sTNF α R2 is a marker for sleep apnea rather than for sex-related differences in sTNF α R2 per

se. A final limitation concerns the applicability of the results to practical decision making in the general population. In the present study, only adults with morbid obesity undergoing bariatric surgery were enrolled. Therefore, these findings may not be applicable to younger and/or less obese populations or to those with stable weight.

Despite these limitations, our study demonstrated that the sTNF α R2 response to massive surgical WL was independently determined by initial sleep apnea severity and by its improvement with WL. The results suggest that increased levels of sTNF α R2 are specific for the sleep apnea over a wide range of body weight. Further prospective studies are needed to explore the dynamic interactions between adipocytokines and sleep apnea.

Acknowledgments

Research Funding Source This study is supported by NIH HL 50381, HL80105, and NCRR UL1 RR 025005. Maria Pallayova is the recipient of a European Respiratory Society Fellowship Number LTRF 15-2008.

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Fig 1. Post-weight loss changes in BMI for the three tertiles of baseline BMI

Fig 2. Individual changes in selected biomarkers following weight loss

Fig 3. Biomarker response to weight loss in subjects stratified by baseline sleep apnea severity

Fig 4.

Prediction plots of biomarker response following weight loss. Predictions of changes in sTNF α R2 and TNF- α /IL-6 ratio are calculated from changes in log-transformed AHI using a linear regression (women—solid diamond, men—solid triangle). The thick line represents the line of best fit for a set of data points. The shaded gray area represents the 95% confidence interval around the best-fit line

Table 1
Baseline and follow-up characteristics of the study population

	No. of obese patients	Before surgery	After surgery	P
Anthropometrics				
BMI, kg/m ²	23	52.3 ±7.4	35.7±6.3	<0.001
Overweight and mild obese, <i>n</i> (%)	23	0	5 (21.7)	0.025
Moderately obese, <i>n</i> (%)	23	0	7 (30.5)	0.008
Severely obese, <i>n</i> (%)	23	1 (4.4)	6 (26.1)	0.059
Morbidly obese, <i>n</i> (%)	23	8 (34.8)	5 (21.7)	0.406
Super obese, <i>n</i> (%)	23	9 (39.1)	0	0.003
Super, super obese, <i>n</i> (%)	23	5 (21.7)	0	0.025
Weight, kg	23	154.4±26.8	103.7±22.8	<0.001
Neck, cm	23	45.8±4.97	38.5±5.09	<0.001
Sagittal abdominal diameter, cm	18	33.6±5.67	26.1±5.27	<0.001
Waist circumference, cm	23	144.8±18.15	109.1 ±18.05	<0.001
Hip circumference, cm	23	149.5± 17.04	119.6±15.85	<0.001
Waist-to-hip ratio	23	0.97±0.09	0.91 ±0.11	0.012
Adipocytokines				
CRP, mg/L	20	10.37 (6.37–13.91)	3.56 (1.65–5.04)	<0.001
IL-1β, pg/mL	23	0.46±0.10	0.45±0.09	0.676
IL-6, pg/mL	23	2.18 (1.63–3.32)	1.26 (0.88–2.08)	0.031
IL-8, pg/mL	23	11.88 (9.92–14.61)	13.43 (11.07–20.74)	0.059
TNF-α, pg/mL	23	2.48±0.76	2.44±0.70	0.662
sTNFαR1, pg/mL	23	3,508.4±1,287.6	2,830.7±1,096.2	0.013
sTNFαR2, pg/mL	23	5,627.5±1,395.0	4,690.5±1,271.5	<0.001
TNF-α/IL-6 ratio	23	1.24±0.58	1.86±0.86	<0.001
Leptin, ng/mL	23	64.97 (48.38–92.44)	26.66 (13.29–47.35)	<0.001
Leptin receptor, ng/mL	23	15.7±2.90	18.9±4.90	0.005
Leptin/leptin receptor ratio	23	4.63 (2.33–5.37)	1.23 (0.69–2.88)	<0.001
Ghrelin, pg/mL	23	687.8 (525.2–811.5)	744.14 (505.7–1,040.7)	0.036
Adiponectin, µg/mL	23	7.18 (5.78–9.88)	11.34 (10.31–14.94)	0.002
Sleep architecture				
Total sleep time, min	23	403.7 (349.8–430.7)	422.3 (392.7–464.1)	0.042
Sleep efficiency, %	23	90 (84–96)	96 (88–97)	0.004
N1, %	23	12.7 (6.0–17.9)	8.9 (5.4–13.7)	0.202
N2, %	23	59.9±12.51	65.0±9.02	0.128
N3, %	23	10.3 (0.4–18.6)	1 (0.2–7.4)	0.003
REM, %	23	14.7±7.52	21.3±6.68	0.006
Polysomnography results				
Total AHI, events/h	23	32.8 (11.4–75.7)	4.7 (2.0–12.9)	<0.001
NREM AHI, events/h	23	23.4 (5.6–75.7)	3.8 (1.2–7)	<0.001
REM AHI, events/h	23	58.8 (30.2–73.6)	12.2 (4.7–27.9)	<0.001

	No. of obese patients	Before surgery	After surgery	<i>P</i>
No sleep apnea, <i>n</i> (%)	23	1 (4.4)	12 (52.2)	0.002
Mild sleep apnea, <i>n</i> (%)	23	6 (26.1)	7 (30.4)	0.781
Moderate sleep apnea, <i>n</i> (%)	23	4 (17.3)	3 (13)	0.705
Severe sleep apnea, <i>n</i> (%)	23	12 (52.2)	1 (4.4)	0.002
Baseline SaO ₂ , %	23	95.2 (94.1–96.1)	96.3 (95.4–97.5)	<0.001
LowSaO ₂ , %	23	89.8 (86–91.7)	92.6 (91–93.6)	<0.001
MinSaO ₂ , %	23	78 (69–84)	86 (80–88)	<0.001
SaO ₂ , %	23	5.5 (4.9–7.7)	3.7 (2.9–5.2)	<0.001

Continuous variables with normal distribution are presented as means±SD if not otherwise stated and compared with use of a Student's *t* test. Continuous variables with non-normal distributions are presented as medians (IQR) and compared with use of the Wilcoxon-matched pairs signed-ranks test. The chi-square test was used to compare categorical variables

N1, *N2*, *N3* stages of NREM sleep, *SaO₂* oxyhemoglobin saturation during sleep, *LowSaO₂* average low oxyhemoglobin saturation during sleep, *MinSaO₂* minimum oxyhemoglobin saturation during sleep, *SaO₂* degree of oxyhemoglobin desaturation associated with each disordered breathing event

Table 2
Sex differences in clinical characteristics

	Women (n=14)	Men (n=9)	P value
Anthropometrics			
Baseline BMI, kg/m ²	51.9±6.01	53.1±9.50	0.710
BMI, kg/m ²	-16.9±4.87	-16.3±7.69	0.815
Baseline neck, cm	42.7±3.20	50.6±3.09	<0.001
neck, cm	-5.9 [-6.8-(-4.3)]	-6.8 [-8.7-(-5.8)]	0.095
Baseline waist circumference, cm	137.2±15.13	156.8±16.42	0.008
waist circumference, cm	-34.7± 13.55	-37.5± 17.18	0.673
Baseline waist-to-hip ratio	0.93 ±0.077	1.04±0.065	0.002
waist-to-hip ratio	-0.07±0.119	-0.03±0.058	0.320
Adipocytokines			
Baseline CRP, mg/L	11.4±5.19	8.7±3.13	0.168
CRP, mg/L	-8.5±4.99	-3.5±3.32	0.038
Baseline TNF-α, pg/mL	2.17±0.525	2.97±0.847	0.011
TNF-α, pg/mL	-0.10 (-0.28-0.07)	-0.03 (-0.40-0.12)	0.753
Baseline sTNFaR1, pg/mL	3,267.6±1,380.8	3,883.0±1,096.4	0.273
sTNFaR1, pg/mL	-222.3 (-1,087-253.5)	-548.9 [-653.3-(-161.9)]	0.795
Baseline sTNFaR2, pg/mL	5,393.2±1,227.8	5,991.9±1,629.8	0.327
sTNFaR2, pg/mL	-974.7±805.2	-878.3±1,611.9	0.850
Baseline leptin, ng/mL	85.35±26.51	46.36±14.10	<0.001
leptin, ng/mL	-39.2 [-79.4-(-33.6)]	-22.4 (-42.3-7.35)	0.078
Baseline leptin receptor, ng/mL	14.9 (12.55-16.60)	16.25 (15.5-16.95)	0.156
leptin receptor, ng/mL	3.75 (-1.8-7.7)	1.75 (-0.6-5.15)	0.706
Baseline leptin/leptin receptor ratio	5.79±1.980	2.83±0.991	<0.001
leptin/leptin receptor ratio	-3.6 [-6.07-(-1.96)]	-1.4[-3.0-(-0.43)]	0.014
Sleep architecture			
Baseline N1, %	9.0±5.93	24.7±15.12	0.002
N1, %	-0.2±5.54	-13.0±15.38	0.009
Baseline N2, %	62.2 ±9.44	56.4±16.19	0.285
N2, %	2.9±13.34	8.6±18.74	0.401
Baseline N3, %	14.4 (8.7-20.3)	0.4 (0-8.6)	0.012
N3, %	-8.5±9.27	-3.4±5.17	0.148
Baseline REM, %	15.1 ±6.08	14.0±9.73	0.734
REM, %	5.9±10.07	7.8±11.57	0.676
Polysomnography results			
Baseline total AHI, events/h	16.9 (10-32.8)	88.7 (61.2-94.6)	0.003
total AHI, events/h	-7.9 [-21.6-(-4.5)]	-63.2 [-91.7-(-43.5)]	0.003
Baseline NREM AHI, events/h	11.8 (5.2-23.4)	95.2 (60.4-101.6)	0.003
NREM AHI, events/h	-5.0 [-14-(-3.2)]	-70.9 [-94.8-(-49.22)]	0.006
Baseline REM AHI, events/h	45.4±25.81	59.2±27.67,646	0.235

	Women (n=14)	Men (n=9)	P value
REM AHI, events/h	-32.4±27.17	-37.0±32.94	0.720

Continuous variables with normal distribution are presented as means±SD and compared with use of a Student's *t* test. Continuous variables with non-normal distributions are presented as medians (IQR) and compared with use of the Wilcoxon rank-sum test

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Table 3
Correlations among post-weight loss changes in biomarkers, AHI, and BMI

	All (n=23)	Women (n=14)	Men (n=9)
AHI with			
Follow-up period	-0.75**	-0.53	-0.94**
CRP	0.13	0.59*	-0.92*
BMI	0.53*	0.64*	0.48
leptin	0.27	0.34	0.42
leptin receptor	-0.28	-0.26	-0.33
leptin/leptin receptor ratio	0.29	0.50	0.17
ghrelin	0.14	0.19	0.17
adiponectin	-0.38	-0.31	-0.67*
IL-1 β	0.24	0.40	-0.13
IL-6	0.58**	0.51	0.67
IL-8	-0.003	-0.02	-0.38
ATNF- α	0.22	0.33	0.17
sTNFaR1	0.35	0.13	0.56
sTNFaR2	0.66**	0.73**	0.74**
TNF- α /IL-6 ratio	-0.75**	-0.70*	-0.87**
BMI with			
Follow-up period	-0.29	-0.63*	0.04
CRP	0.23	0.50	-0.11
leptin	0.33	0.57*	0.14
leptin receptor	-0.29	-0.45	0.25
leptin/leptin receptor ratio	0.33	0.81**	-0.25
ghrelin	-0.10	-0.12	-0.30
adiponectin	-0.28	-0.62*	-0.13
IL-1 β	0.19	0.30	0.08
IL-6	0.27	0.25	0.36
IL-8	-0.21	-0.34	-0.40
ATNF- α	0.08	0.28	0.05
sTNFaR1	0.21	0.26	-0.03
sTNFaR2	0.38	0.69*	0.22
TNF- α /IL-6 ratio	-0.50*	-0.60*	-0.51

The Pearson product-moment correlation coefficients and Spearman's rank correlation coefficients

* $P < 0.05$;

** $P < 0.005$