Effect of Weight Loss on Upper Airway Anatomy and the Apnea Hypopnea Index: The Importance of Tongue Fat

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ONLINE SUPPLEMENT

SUPPLEMENTAL METHODS

Subjects

The study used a prospective design of persons with obesity and sleep apnea and who presented for either bariatric surgery or a lifestyle modification intervention for their obesity. Study participants were recruited from the Penn Center for Sleep Disorders outpatient practice and from patients seeking weight-loss treatment at the University of Pennsylvania's Bariatric Surgery Program or a lifestyle modification intervention at the Center for Weight and Eating Disorders. The study was approved by the University of Pennsylvania Institutional Review Board for human studies (protocols 808496 and 809398), and written informed consent was obtained from all participants. All participants were greater than 18 years old and had an apnea-hypopnea index (AHI) ≥10 events/hour as determined by polysomnography which were the criteria used in our previous study examining tongue fat in controls and apneics without weight loss (E1). Exclusion criteria included inability to undergo upper airway and abdominal magnetic resonance imaging (MRI) or pregnancy. Participants underwent an MRI and in-laboratory sleep study before beginning weight loss treatment. Participants returned after 6 months for a follow-up MRI and in-laboratory sleep study.

Medical and Surgical Weight Loss Protocols

Participants undergoing a lifestyle modification program for weight loss (n=49) or bariatric surgery (n=18) were invited to participate. Patients undergoing bariatric surgery had gastric sleeve procedure (n=8), gastric bypass (Roux-en-Y) (n=9) or gastric banding (n=1). The lifestyle modification program was based upon the Diabetes Prevention Program and designed to promote a weight loss of 5-10% of initial body weight through caloric restriction, increased physical activity, and behavioral modification strategies (E2). The calorie goals were 1200-1500 kcal/day for those who weighed <250 pounds, and 1500-1800 kcal/day for those whose weight exceeded 250 pounds. Dietary composition was aligned with that recommended by the NHLBI guidelines on the treatment of obesity (E2) and included recommendations to consume <7% saturated fat, <10% polyunsaturated fat, <20% monounsaturated fats, 25-30% total fat, 50-60% carbohydrates, and 15% protein. Participants were prescribed a program of physical activity consisting of walking 4 times per week, starting at 10 minutes per session and building to 30 minutes per session over a 12-week period. Participants had 30-minute individual sessions with a registered dietitian with extensive experience in behavioral weight control counseling. Each patient received 24 weekly individual counseling sessions during the 6-month treatment period. Participants were instructed on how to comply with the dietary prescription and in traditional behavioral methods of weight control such as self-monitoring, stimulus control, slow eating, and related behaviors.

Magnetic Resonance Imaging (MRI)

Upper airway and abdominal MRI studies were acquired using a 1.5 Tesla MAGNETOM Espree scanner (Siemens Medical Systems, Malvern, PA), as described in our previous publications (E1, E3-5). Three different imaging sequences were utilized as reported in our previous publications: 1) T1-weighted spin echo imaging (for airway and surrounding upper airway soft tissue structures) (E3, E5); 2) Dixon imaging for tongue fat measurements (E1); and 3) T1-weighted gradient recalled echo imaging for abdominal fat imaging (E4).

Analysis of the Upper Airway, Surrounding Soft Tissue Structures and Abdominal Fat

The MRI analysis was performed twice (baseline and after 6 months) and split into 3 different domains: 1) *upper airway analysis* (airway volume, average cross-sectional area, minimum airway area, minimum anterior-posterior distance and minimum lateral distance) in the retropalatal (RP) and retroglossal (RG) regions; 2) *volumetric analysis of the upper airway soft tissues structures* (tongue, tongue fat, soft palate, parapharyngeal fat pads, lateral walls, pterygoids, epiglottis, and combined soft tissue volume [equal to the sum of these structures]); and 3) *abdominal fat volumes* (total, subcutaneous and visceral). As previously described, Amira 4.1.2 image analysis software (Visage Imaging, San Diego, CA), was utilized to quantify the upper airway, the surrounding soft tissue structures (E1, E5, E6), tongue fat (1) and abdominal subcutaneous/visceral fat (E4). Amira is a software program that allows the technician to segment the upper airway soft tissues structures using thresholding based on grayscale of the specific tissue (tongue, pharyngeal lateral walls, parapharyngeal fat pads, etc). Amira requires the technician to outline the pharyngeal structures. The technician was blinded to the pre-post-weight loss status of the patients and performed the analysis in the same manner in each subject. We have shown that our upper airway soft tissue and tongue fat analysis measurements are reproducible and accurate (E1, E5). Accuracy of our fat volume estimates have been assessed previously (E1) by performing Dixon MRI of a hamburger and steak before and after injection of a known volume of fat (lard) into the tissue (6 cc added to the steak and 3 cc added to the hamburger) and comparing the results to the known quantity.

Although fat-weighted Dixon images provide a reproducible objective measure adipose tissue, the boundaries of soft tissues with Dixon imaging are not as distinct in comparison to the standard spin-echo images (E1). Therefore the boundaries of the tongue on each MR axial slice was determined on standard axial T1 spin-echo MR images, and then superimposed onto the axial Dixon fat-only MR images in order to select all fat within that region.. The grayscale setting to segment tongue fat was chosen based on the grayscale intensity of the surrounding subcutaneous and neck fat allowing us to standardize the tongue fat intensity across all subjects (E1). We have shown that this analysis technique for tongue fat is highly reproducible (E1). The technician performing these MRI analyses was blinded to polysomnography results and the pre-post weight loss state of each subject.

Reproducibility Assessment

To understand the reproducibility of MRI analyses, we compared measurements quantified from MRIs performed 6 months apart in an available sample of 17 individuals (n=13 OSA, 4 non-OSA) that were weight stable over the follow-up period (defined as follow-up weight within 2.5% of baseline weight). Using these repeated measurements, we calculated the intraclass correlation coefficient (ICC) for each of our anatomy measures of interest. As suggested by Landis and Koch (E7), ICC value ranges can be used to qualitatively assess level of reproducibility as *poor* (<0.00), *slight* (0.00-0.20), *fair* (0.21-0.40), *moderate* (0.41-0.60), *substantial* (0.61-0.80) and *almost perfect* (0.81-1.00).

Statistical Analysis

Data are summarized using means and standard deviations (continuous) or frequencies and percentages (categorical). To summarize changes over the follow-up period, we calculated subject-specific percentage and absolute change scores as follow-up minus baseline values. Primary analyses examining the relationship between weight loss and anatomic changes were performed using Pearson's correlations, unadjusted and controlling for relevant baseline covariates (age, sex, race, height and AHI). Associations between change in upper airway anatomy (or weight) and change in AHI were performed in a similar manner. These analyses were performed unadjusted, controlling for clinical covariates, and further adjusted for percentage change in weight to assess whether individual structures were associated with changes in AHI independent of change in weight. As a complementary analysis, we also quantified and compared change scores in patients that lost at least 2.5% weight and those that were stable or gained weight. Comparisons between groups were performed using T-tests or linear regression models with and without covariate adjustment. In addition to the above covariates, baseline values of the variable of interest were included in models comparing absolute change between groups. Significance of within group changes were assessed with paired T-tests. Where presented, statistical comparisons of correlation coefficients were performed by deriving a non-parametric p-value based on the observed distribution of differences in correlations from 1,000 bootstrapped samples (E8, E9).

To test whether associations between percent weight change and percent AHI improvements are mediated by specific upper airway or soft tissue anatomy percent changes, we utilized mediation modeling (E10). Mediation analyses were conducted by PROCESS, a conditional process modeling program that utilizes an ordinary least squares path analytical framework to test for both direct and indirect effects (E11). To comprehensively examine upper airway mediators, we first tested all putative mediators individually using single mediator models. Based on the results of these single mediator models, we then created a combined, parallel multiple mediator model including any significant individual mediators to examine the most influential mediators in the presence of all possible mediators (see **Figure S1** for hypothesized mediation models). Bias-corrected 95% confidence intervals (CIs) were estimated using bootstrapping (n=5000 samples) to verify indirect (mediating) effects; estimates are presented unstandardized and standardized (to allow direct comparison of indirect effects across proposed mediators). The indirect effect was considered significant and mediation demonstrated if this confidence interval did not contain zero. (E10, E12). This approach computes more accurate confidence intervals of indirect effects than other commonly used methods (E10) and provides higher power while maintaining control over the Type I error rate (E13). Baseline age, sex, race, and height were controlled for all mediation models.

We utilized a domain-specific Hochberg correction (E14-16) to control for multiple comparisons when determining statistical significance of associations with individual upper airway anatomical measures. As described by Hochberg and Benjamini (E15), for a given set of *m* hypotheses:

> *This procedure starts by examining the largest p-value* $P_{(m)}$*. If* $P_{(m)} \leq \alpha$*, then* $H_{(m)}$ *and all other hypotheses are rejected. If not,* $H_{(m)}$ *is not rejected and one proceeds to compare* $P_{(m-1)}$ *with* $\alpha/2$*.*

If the former is smaller, then $H_{(m-1)}$ and all hypotheses with smaller p-values are rejected. Generally, one proceeds from highest to lower p-values, retaining $H_{(i)}$ if its p-value satisfies $P_{(i)} > \alpha/(m - i + 1)$. One stops the procedure at the first ordered hypothesis when that inequality is reversed. This hypothesis is rejected and so are all hypotheses with lower or equal p-values.

In addition to this approach for determining statistically significant results, any unadjusted $p<0.05$ was considered nominally significant evidence. Significance in multivariate models was assessed using the confidence interval approach, detailed above. Analyses were conducted using Stata, Version 14 (StataCorp LP, College Station, TX), SAS Software Version 9.4 (SAS Institute Inc., Cary, NC) and SPSS 24 (IBM Corp., Armonk, NY).

Our sample size of 67 apneics provided adequate power (80%) for detecting correlations of 0.34 at a nominal level of significance ($p<0.05$). Similarly, in analyses comparing apneics who lost weight (n=47) to those who were weight stable or gained weight (n=20), we had at least 80% power to detect standardized differences of 0.76. These correspond to moderate or large effects as defined by Cohen (E17). Thus, the study was powered for meaningful effect sizes. Non-significant associations for smaller effect sizes should be interpreted with some caution, as it is possible that these represent real associations that the current sample is underpowered to declare significant (e.g., false negatives).

SUPPLEMENTAL RESULTS

Patient characteristics of weight loss groups

Demographic characteristics of the sample are shown in **Table 1**. Forty-seven (70.1%) patients lost ≥2.5% body weight (average change -14.5±8.5% [p<0.0001]), compared to 20 (29.9%) that were weight stable or gained weight (average change 2.3±4.5% [p=0.036]). Patients who lost weight had a significant AHI reduction (-23.3±21.9; p<0.0001), compared to no change in those that did not (p=0.856).

Comparison of weight loss interventions

All participant in the bariatric surgery arm (n=18) lost at least 2.5% body weight, while in those undergoing lifestyle modification a total of 29 (59.2%) lost at least 2.5% body weight and 20 (40.8%) were weight stable or gained weight. Among participants that lost weight, those that underwent bariatric surgery had greater weight loss than those that underwent intensive lifestyle modification (-19.2±6.8% vs. -11.6±8.2%, p=0.002). Relatedly, there was greater improvement in AHI among patients who lost weight with bariatric surgery than those who lost weight with intensive lifestyle modification (-73.8±17.8% vs. -49.6±36.5%, p=0.004).

Changes in Upper Airway Anatomy in Weight Loss and Weight Stable/Gain Patients

Airway Sizes

Secondary comparisons of percent changes in airway size between weight loss and weight stable/gain patients are shown in **Table S3A**. Patients who lost ≥2.5% weight showed increased retropalatal airway volume (p=0.007), cross-sectional area (p=0.001), minimum area (p=0.003) and minimum lateral distance (p=0.001), as well as a large increase in retroglossal minimum area (p=0.001). After covariate adjustment, differences in the percentage changes in the RP minimum lateral distance (p=0.020) and RG minimum area (p=0.023) were nominally different between weight loss groups

(**Table S3A**). Similar results were observed when comparing absolute changes (**Table S4A**), although the increased RG minimum area was nominal (p=0.032) among the weight loss group. There was also a significant absolute decrease in RP minimum AP distance (p=0.003) among the weight loss group. After adjustment, differences in RP minimum AP (p=0.022) and lateral (p=0.033) distance remained nominally different between groups.

Soft Tissue Volumes

Supporting results observed in correlational analysis, most soft tissue measures showed significant decreases in volume among patients with OSA who lost weight (**Table S3B**), including combined soft tissue (p<0.0001), genioglossus (p=0.001), tongue fat (p<0.0001), total tongue (p=0.009), fat pads (p<0.0001), pterygoid (p<0.0001), RP lateral walls (p<0.0001) and total lateral walls (p<0.0001). Compared to patients without weight loss, there were significant differences in the change in tongue fat volume (p<0.0001), pterygoid volume (p=0.001) and total lateral wall volume (p=0.001). Differences remained significant controlling for covariates (**Table S3B**). Similar results were observed for absolute changes (**Tables S4B**); in adjusted analyses, we also observed a significant difference in the absolute change in fat pad volume between groups (p=0.004).

Abdominal Fat Volumes

Among patients who lost ≥2.5% weight, there were large percentage reductions in each measurement (**Table S3C**), compared to no significant changes in those who did not lose weight. Differences between groups were statistically significant in adjusted analyses. Similar results were seen for absolute changes (**Table S4C**), with significant differences between groups in adjusted analysis.

Associations between Changes in Tongue Fat and Abdominal Fat

Given correlations between percent change in weight and percent changes in tongue and abdominal fat volumes, we assessed the correlations between tongue and abdominal fat changes. In covariate adjusted analyses, percentage change in tongue fat was positively associated with percentage changes in total (partial rho = 0.48, p=0.005), subcutaneous (partial rho = 0.40, p=0.021), and visceral (partial rho = 0.55, p=0.0009) fat volumes. Correlations between the percentage changes in tongue fat and both total abdominal fat (p=0.034) and subcutaneous abdominal fat (p=0.026), but not visceral abdominal fat (p=0.154), were smaller than the correlation between percentage changes in tongue fat and weight. Thus, there is some evidence of a stronger relationship of percent changes in tongue fat with changes in weight.

Figure E1. *Illustration of hypothesized single and multiple mediation models.* The hypothesized mediation models examined through conditional process analysis are illustrated. In particular, the direct effect of percent change in weight on percentage change in AHI (*path c*) is shown in the top schematic. The middle schematic shows the evaluated single mediator model of mediation by an individual upper airway variable, including the relationship between weight percent change and anatomy (*path a*), between anatomy and percentage change in AHI (*path b*) and the remaining direct effect of weight percent change on AHI percent change (*path c'*). Finally, the single mediator model is extended to show the hypothesized multiple mediator model, including *N* single mediators with specific individual a_N and b_N path effects.

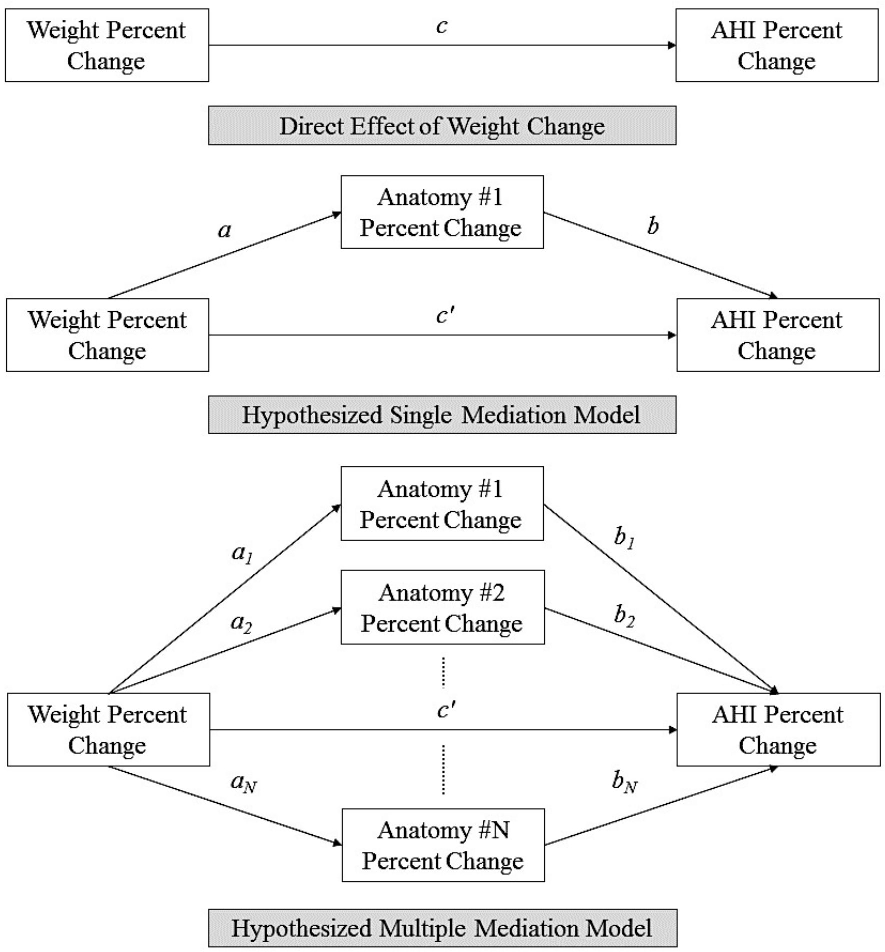

Table E1: Intraclass Correlation Coefficients for MRI Variables Among a Weight Stable Population

Measure	Weight Stable Participants	
	N	ICC†
RP Airway Volume	17	0.777
RP Cross Sectional Area	17	0.808
RP Minimum Area	17	0.935
RP Minimum AP Distance	17	0.701
RP Minimum Lateral Distance	17	0.889
RG Airway Volume	14	0.844
RG Cross Sectional Area	14	0.856
RG Minimum Area	15	0.849
RG Minimum AP Distance	15	0.746
RG Minimum Lateral Distance	15	0.829
Total Soft Tissue Volume	17	0.944
Soft Palate Volume	17	0.779
Genioglossus Volume	17	0.922
Other Tongue Volume	17	0.721
Tongue Fat Volume	11	0.979
Total Tongue Volume	17	0.946
Epiglottis Volume	17	0.750
Fat Pads Volume	17	0.353
Pterygoid Volume	17	0.694
RP Lateral Walls Volume	17	0.911
RG Lateral Walls Volume	17	0.758
Total Lateral Walls Volume	17	0.910
Abdominal Total Fat Volume	14	0.489
Abdominal Subcutaneous Fat Volume	14	0.536
Abdominal Visceral Fat Volume	14	0.751

†Intraclass correlation coefficient (ICC) presented as a measure of reproducibility of the indicated measure over time among weight stable individuals; As suggested by Landis and Koch (23), ICC value ranges can be used to qualitatively assess level of agreement as *poor* (<0.00), *slight* (0.00-0.20), *fair* (0.21-0.40), *moderate* (0.41-0.60), *substantial* (0.61-0.80) and *almost perfect* (0.81-1.00). Abbreviations: ICC = intraclass correlation coefficient; RP = retropalatal; RG = retroglossal

Table E2A: Pearson's Correlations between Absolute Change in Weight and Absolute Change in Airway Size among Patients with OSA

Airway Sizes	**Unadjusted**			**Adjusted**		
	N	**rho†**	**p**	**N**	**rho‡**	**p**
RP Airway Volume	64	-0.16	0.211	63	-0.21	0.110
RP Cross Sectional Area	64	-0.21	0.103	63	-0.27	0.037
RP Minimum Area	64	-0.03	0.789	63	-0.05	0.688
RP Minimum AP Distance	**64**	**0.36**	**0.003**	**63**	**0.49**	**0.0001**
RP Minimum Lateral Distance	64	-0.33	0.008	**63**	**-0.40**	**0.002**
RG Airway Volume	62	0.08	0.535	61	0.11	0.434
RG Cross Sectional Area	60	0.06	0.662	59	0.04	0.761
RG Minimum Area	61	-0.01	0.934	60	-0.13	0.335
RG Minimum AP Distance	60	0.26	0.046	59	0.24	0.078
RG Minimum Lateral Distance	60	-0.03	0.842	59	-0.04	0.757

†Unadjusted Pearson's linear correlations; ‡Partial Pearson's correlation adjusted for age, gender, race, AHI and height. Significant values after Hochberg correction shown in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E2B: Pearson's Correlations between Absolute Change in Weight and Absolute Change in Soft Tissue Volumes among Patients with OSA

Soft Tissue Volumes	**Unadjusted**			**Adjusted**		
	N	**rho†**	**p**	**N**	**rho‡**	**p**
Combined Soft Tissue	63	0.09	0.488	62	0.10	0.456
Soft Palate	64	-0.12	0.338	63	-0.12	0.363
Genioglossus	64	-0.03	0.825	63	-0.03	0.799
Other Tongue	64	-0.06	0.649	63	-0.03	0.811
Tongue Fat	**52**	**0.47**	**0.0004**	**51**	**0.48**	**0.001**
Total Tongue	64	-0.06	0.639	63	-0.05	0.727
Epiglottis	63	0.04	0.737	62	0.06	0.632
Fat Pads	63	0.06	0.631	62	0.04	0.787
Pterygoid	**64**	**0.37**	**0.002**	63	0.37	0.005
RP Lateral Walls	64	0.16	0.212	63	0.15	0.267
RG Lateral Walls	64	0.17	0.171	63	0.22	0.094
Total Lateral Walls	64	0.24	0.054	63	0.28	0.035

†Unadjusted Pearson's linear correlations; ‡Partial Pearson's correlation adjusted for age, gender, race, AHI and height. Significant values represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E2C: Pearson's Correlations between Absolute Change in Weight and Absolute Change in Abdominal Fat Measures among Patients with OSA

Abdominal Fat Volume	**Unadjusted**			**Adjusted**		
	N	**rho†**	**p**	**N**	**rho‡**	**p**
Abdominal Total Fat	**51**	**0.57**	**<0.0001**	**50**	**0.58**	**<0.0001**
Abdominal Subcutaneous Fat	**51**	**0.56**	**<0.0001**	**50**	**0.57**	**<0.0001**
Abdominal Visceral Fat	**51**	**0.49**	**0.0003**	**50**	**0.54**	**0.0001**

†Unadjusted Pearson's linear correlations; ‡Partial Pearson's correlation adjusted for age, gender, race, AHI and height. Significant values represented in **bold**.

Table E3A: Percent Changes in Airway Size in Patients with OSA based on weight change

Airway Sizes	Weight Stable/Gain			Weight Loss			p_{unadj} ‡	p_{adj} §
	N	Mean ± SD	p†	N	Mean ± SD	p†		
RP Airway Volume	19	13.8 ± 47.0	0.216	**45**	**21.5 ± 51.3**	**0.007**	0.579	0.512
RP Cross Sectional Area	19	15.4 ± 42.0	0.127	**45**	**24.4 ± 47.5**	**0.001**	0.475	0.374
RP Minimum Area	19	17.8 ± 58.1	0.197	**45**	**55.9 ± 116.7**	**0.003**	0.088	0.158
RP Minimum AP Distance	19	9.7 ± 42.6	0.332	45	-3.1 ± 77.3	0.789	0.399	0.426
RP Minimum Lateral Distance	19	1.1 ± 30.6	0.879	**45**	**33.8 ± 65.6**	**0.001**	0.009	0.020
RG Airway Volume	17	19.6 ± 29.6	0.015	45	7.8 ± 35.7	0.149	0.230	0.317
RG Cross Sectional Area	17	19.6 ± 36.4	0.042	43	6.3 ± 28.7	0.160	0.140	0.197
RG Minimum Area	17	21.7 ± 57.1	0.136	**44**	**424.6 ± 778.8**	**0.001**	**0.001**	0.023
RG Minimum AP Distance	17	8.1 ± 40.4	0.421	43	7.0 ± 48.2	0.343	0.938	0.998
RG Minimum Lateral Distance	17	13.3 ± 44.3	0.233	43	16.3 ± 54.4	0.055	0.840	0.668

†p-value from paired T-test examining significance of within group change; ‡p-value from T-test comparing changes between weight loss and weight stable/gain; §p-value adjusted for age, sex, race, AHI and height. Significant values after Hochberg correction represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E3B: Percent Changes in Soft Tissue Volumes in Patients with OSA based on weight change

Soft Tissue Volumes	Weight Stable/Gain			Weight Loss			p_{unadj} ‡	p_{adj} §
	N	Mean ± SD	p†	N	Mean ± SD	p†		
Combined Soft Tissue	19	-3.3 ± 6.3	0.035	**44**	**-7.4 ± 9.0**	**<0.0001**	0.077	0.057
Soft Palate	19	-8.6 ± 22.7	0.115	45	-0.1 ± 24.0	0.986	0.190	0.197
Genioglossus	19	-3.0 ± 7.3	0.092	**45**	**-5.1 ± 10.0**	**0.001**	0.409	0.318
Other Tongue	19	-2.4 ± 25.0	0.682	45	-0.8 ± 28.4	0.859	0.828	0.951
Tongue Fat	13	6.8 ± 11.5	0.055	**39**	**-19.9 ± 17.8**	**<0.0001**	**<0.0001**	**<0.0001**
Total Tongue	19	-3.7 ± 6.5	0.023	**45**	**-4.6 ± 11.4**	**0.009**	0.692	0.577
Epiglottis	19	14.7 ± 38.2	0.111	44	3.6 ± 40.1	0.557	0.309	0.211
Fat Pads	19	-15.9 ± 26.0	0.016	**44**	**-28.3 ± 22.2**	**<0.0001**	0.058	0.078
Pterygoid	19	1.5 ± 16.9	0.704	**45**	**-12.0 ± 13.4**	**<0.0001**	**0.001**	**0.004**
RP Lateral Walls	19	-2.6 ± 16.4	0.504	**45**	**-11.9 ± 15.1**	**<0.0001**	0.032	0.022
RG Lateral Walls	19	14.3 ± 22.0	0.011	45	-2.8 ± 24.2	0.441	0.010	0.020
Total Lateral Walls	19	3.4 ± 14.8	0.333	**45**	**-9.3 ± 11.8**	**<0.0001**	**0.001**	**0.001**

†p-value from paired T-test examining significance of within group change; ‡p-value from T-test comparing changes between weight loss and weight stable/gain; §p-value adjusted for age, sex, race, AHI and height. Significant values after Hochberg correction represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E3C: Percent Changes in Abdominal Fat Volumes in Patients with OSA based on weight change

Abdominal Fat Volume	Weight Stable/Gain			Weight Loss			p_{unadj} ‡	p_{adj} §
	N	Mean ± SD	p†	N	Mean ± SD	p†		
Abdominal Total Fat	15	-0.1 ± 38.4	0.991	**36**	**-21.1 ± 17.8**	**<0.0001**	0.059	**0.013**
Abdominal Subcutaneous Fat	15	-1.4 ± 36.0	0.883	**36**	**-19.4 ± 18.2**	**<0.0001**	0.084	**0.024**
Abdominal Visceral Fat	15	9.5 ± 64.4	0.576	**36**	**-25.9 ± 21.6**	**<0.0001**	0.055	**0.007**

†p-value from paired T-test examining significance of within group change; ‡p-value from T-test comparing changes between weight loss and weight stable/gain; §p-value adjusted for age, sex, race, AHI and height. Significant values after Hochberg correction represented in **bold.**

Table E4A: Absolute Changes in Airway Size in Patients with OSA based on weight change

Airway Sizes	Weight Stable/Gain			Weight Loss			p_{unadj}‡	p_{adj}§
	N	Mean ± SD	p†	N	Mean ± SD	p†		
RP Airway Volume, mm^3	19	103.8 ± 1773.5	0.802	45	377.2 ± 1434.5	0.085	0.519	0.754
RP Cross Sectional Area, mm^2	19	32.0 ± 134.3	0.312	45	53.1 ± 125.6	0.007	0.551	0.632
RP Minimum Area, mm^2	19	3.3 ± 23.1	0.547	45	13.4 ± 39.1	0.027	0.205	0.232
RP Minimum AP Distance, mm	19	0.47 ± 3.23	0.533	**45**	**-3.54 ± 7.52**	**0.003**	**0.004**	0.022
RP Minimum Lateral Distance, mm	19	-0.26 ± 2.42	0.642	**45**	**2.24 ± 4.79**	**0.003**	0.008	0.033
RG Airway Volume, mm^3	17	1030.8 ± 1823.3	0.033	45	-25.9 ± 2395.0	0.943	0.105	0.286
RG Cross Sectional Area, mm^2	17	88.7 ± 242.7	0.151	43	18.5 ± 195.6	0.539	0.247	0.379
RG Minimum Area, mm^2	17	16.9 ± 81.3	0.404	44	39.6 ± 118.6	0.032	0.471	0.848
RG Minimum AP Distance, mm	17	0.26 ± 4.42	0.813	43	-0.52 ± 4.49	0.456	0.548	0.220
RG Minimum Lateral Distance, mm	17	0.23 ± 5.57	0.866	43	0.72 ± 6.10	0.443	0.776	0.944

†p-value from paired T-test examining significance of within group change; ‡p-value from T-test comparing changes between weight loss and weight stable/gain; §p-value adjusted for age, sex, race, AHI, height and baseline airway size. Significant values after Hochberg correction represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E4B: Absolute Changes in Soft Tissue Volumes in Patients with OSA based on weight change

Soft Tissue Volumes (mm^3)	Weight Stable/Gain			Weight Loss			p_{unadj}‡	p_{adj}§
	N	Mean ± SD	p†	N	Mean ± SD	p†		
Combined Soft Tissue	19	-6959.9 ± 11999.6	0.021	**44**	**-15100.3 ± 19816.8**	**<0.0001**	0.050	0.054
Soft Palate	19	-894.0 ± 1866.5	0.051	45	-191.4 ± 1746.8	0.466	0.155	0.381
Genioglossus	19	-3014.8 ± 7137.1	0.082	**45**	**-5284.8 ± 10333.8**	**0.001**	0.387	0.306
Other Tongue	19	-2286.4 ± 9895.2	0.327	45	-1197.6 ± 10204.6	0.435	0.695	0.444
Tongue Fat	13	1864.4 ± 3173.6	0.056	**39**	**-5536.7 ± 5110.1**	**<0.0001**	**<0.0001**	**0.0001**
Total Tongue	19	-5301.2 ± 8809.8	0.017	**45**	**-6482.4 ± 16082.5**	**0.010**	0.708	0.512
Epiglottis	19	124.3 ± 544.3	0.333	44	-33.5 ± 613.7	0.719	0.337	0.028
Fat Pads	19	-1504.5 ± 2276.3	0.010	**44**	**-2219.8 ± 1927.1**	**<0.0001**	0.206	**0.004**
Pterygoid	19	232.8 ± 4043.8	0.805	**45**	**-3149.4 ± 3444.5**	**<0.0001**	**0.001**	**0.0002**
RP Lateral Walls	19	-684.4 ± 2108.1	0.174	**45**	**-1795.2 ± 2381.8**	**<0.0001**	0.083	0.016
RG Lateral Walls	19	1067.2 ± 2065.4	0.037	45	-807.4 ± 3044.4	0.082	0.017	0.040
Total Lateral Walls	19	382.8 ± 2808.7	0.560	**45**	**-2602.7 ± 3566.0**	**<0.0001**	**0.002**	**0.001**

†p-value from paired T-test examining significance of within group change; ‡p-value from T-test comparing changes between weight loss and weight stable/gain; §p-value adjusted for age, sex, race, AHI, height and baseline soft tissue volume. Significant values after Hochberg correction represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E4C: Absolute Changes in Abdominal Fat Volumes in Patients with OSA based on weight change

Abdominal Fat Volume (mm^3)	Weight Stable/Gain			Weight Loss			p_{unadj}‡	p_{adj}§
	N	Mean ± SD	p†	N	Mean ± SD	p†		
Abdominal Total Fat	15	-1337194 ± 6041271	0.406	**36**	**-3825576 ± 4108429**	**<0.0001**	0.094	**0.002**
Abdominal Subcutaneous Fat	15	-1019828 ± 4808678	0.425	**36**	**-2898336 ± 3418169**	**<0.0001**	0.120	**0.006**
Abdominal Visceral Fat	15	-317367 ± 1441512	0.408	**36**	**-927240 ± 958480**	**<0.0001**	0.082	**0.001**

†p-value from paired T-test examining significance of within group change; ‡p-value from T-test comparing changes between weight loss and weight stable/gain; §p-value adjusted for age, sex, race, AHI, height and baseline abdominal fat volume. Significant values after Hochberg correction represented in **bold.**

Table E5A: Correlations between Absolute Change in AHI and Absolute Change in Airway Size among Patients with OSA

Airway Sizes	Unadjusted			Adjusted Results: Covariates Only†			Adjusted Results: Covariates and Weight Change‡		
	N	rho†	p	N	rho‡	p	N	rho§	p
RP Airway Volume	63	0.15	0.241	62	0.08	0.576	62	0.24	0.077
RP Cross Sectional Area	63	0.12	0.347	62	0.05	0.737	62	0.24	0.067
RP Minimum Area	63	-0.04	0.726	62	-0.05	0.712	62	-0.03	0.833
RP Minimum AP Distance	63	0.26	0.038	62	0.30	0.022	62	0.04	0.762
RP Minimum Lateral Distance	63	-0.17	0.173	62	-0.18	0.183	62	0.06	0.681
RG Airway Volume	61	-0.12	0.371	60	-0.14	0.292	60	-0.23	0.090
RG Cross Sectional Area	59	0.02	0.867	58	0.00	0.973	58	-0.02	0.873
RG Minimum Area	60	-0.06	0.657	59	-0.07	0.601	59	0.00	0.977
RG Minimum AP Distance	59	0.12	0.347	58	0.16	0.249	58	0.01	0.944
RG Minimum Lateral Distance	59	-0.10	0.429	58	-0.23	0.102	58	-0.22	0.107

†Unadjusted Pearson's linear correlation; ‡Partial Pearson's correlation adjusted for age, gender, race and height; §Partial Pearson's correlation adjusted for age, gender, race, height and percent change in weight. Significant values after Hochberg correction represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E5B: Correlations between Absolute Change in AHI and Absolute Change in Soft Tissues among Patients with OSA

Soft Tissue Volumes	Unadjusted			Adjusted Results: Covariates Only†			Adjusted Results: Covariates and Weight Change‡		
	N	rho†	p	N	rho‡	p	N	rho§	p
Combined Soft Tissue	62	0.09	0.482	61	0.05	0.698	61	0.01	0.913
Soft Palate	63	-0.06	0.625	62	-0.08	0.554	62	-0.01	0.944
Genioglossus	63	0.03	0.794	62	0.05	0.735	62	0.09	0.507
Other Tongue	63	-0.04	0.734	62	-0.07	0.618	62	-0.05	0.721
Tongue Fat	**51**	**0.47**	**0.001**	**50**	**0.47**	**0.001**	50	0.29	0.057
Total Tongue	63	-0.01	0.947	62	-0.02	0.901	62	0.03	0.846
Epiglottis	62	0.13	0.316	61	0.08	0.539	61	0.06	0.673
Fat Pads	62	0.09	0.501	61	0.09	0.483	61	0.09	0.505
Pterygoid	63	0.28	0.024	62	0.19	0.148	62	-0.02	0.903
RP Lateral Walls	63	0.30	0.018	62	0.25	0.061	62	0.21	0.120
RG Lateral Walls	63	-0.05	0.697	62	-0.10	0.448	62	-0.25	0.058
Total Lateral Walls	63	0.15	0.233	62	0.07	0.594	62	-0.08	0.574

†Unadjusted Pearson's linear correlation; ‡Partial Pearson's correlation adjusted for age, gender, race and height; §Partial Pearson's correlation adjusted for age, gender, race, height and percent change in weight. Significant values after Hochberg correction represented in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E5C: Correlations between Absolute Change in AHI and Absolute Change in Abdominal Fat Measures among Patients with OSA

Abdominal Fat Volume	Unadjusted			Adjusted Results					
				Covariates Only			Covariates and Weight Change		
	N	rho†	p	N	rho‡	p	N	rho§	p
Abdominal Total Fat	50	0.31	0.029	**49**	**0.34**	**0.021**	49	0.03	0.829
Abdominal Subcutaneous Fat	50	0.28	0.051	**49**	**0.33**	**0.027**	49	0.02	0.880
Abdominal Visceral Fat	**50**	**0.35**	**0.012**	**49**	**0.34**	**0.024**	49	0.06	0.702

†Unadjusted Pearson's linear correlation; ‡Partial Pearson's correlation adjusted for age, gender, race and height; §Partial Pearson's correlation adjusted for age, gender, race, height and change in weight. Significant values after Hochberg correction represented in **bold**.

Table E6A: Partial Pearson's correlations between Percent Change in Positional AHI and Percent Change in Airway Size among Patients with OSA†

Airway Sizes	Supine AHI						Non-Supine AHI					
	Covariates Only			Covariates and Weight Change			Covariates Only			Covariates and Weight Change		
	N	rho‡	p	N	rho§	p	N	rho‡	p	N	rho§	p
RP Airway Volume	36	0.13	0.490	36	0.10	0.610	47	0.00	0.988	47	0.03	0.831
RP Cross Sectional Area	36	0.11	0.548	36	0.06	0.734	47	-0.05	0.771	47	0.03	0.832
RP Minimum Area	36	-0.01	0.958	36	-0.00	0.997	47	-0.07	0.669	47	-0.08	0.593
RP Minimum AP Distance	36	-0.11	0.538	36	-0.06	0.746	47	0.18	0.236	47	-0.02	0.923
RP Minimum Lateral Distance	36	0.08	0.652	36	0.04	0.814	47	-0.20	0.196	47	0.06	0.727
RG Airway Volume	35	-0.09	0.638	35	-0.10	0.583	45	0.12	0.463	45	0.06	0.696
RG Cross Sectional Area	33	-0.02	0.901	33	-0.04	0.826	43	0.33	0.041	43	0.25	0.138
RG Minimum Area	34	0.30	0.111	34	0.22	0.246	44	-0.31	0.055	44	0.15	0.364
RG Minimum AP Distance	33	-0.04	0.817	33	-0.03	0.879	44	0.22	0.166	44	0.12	0.457
RG Minimum Lateral Distance	33	-0.18	0.337	33	-0.19	0.339	44	0.09	0.584	44	0.14	0.387

†Analyses restricted to subsets of patients with specific positional AHI ≥ 5 events/hour at baseline; ‡Partial Pearson's correlation adjusted for age, gender, race and height; §Partial Pearson's correlation adjusted for age, gender, race, height and percent change in weight. Significant values after Hochberg correction shown in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E6B: Partial Pearson's Correlations between Percent Change in Positional AHI and Percent Change in Soft Tissues among Patients with OSA

Soft Tissue Volumes	Supine AHI						Non-Supine AHI					
	Covariates Only			Covariates and Weight Change			Covariates Only			Covariates and Weight Change		
	N	**rho‡**	**p**	**N**	**rho§**	**p**	**N**	**rho‡**	**p**	**N**	**rho§**	**p**
Combined Soft Tissue	35	-0.11	0.568	35	-0.10	0.614	47	0.16	0.307	47	-0.11	0.498
Soft Palate	36	0.22	0.220	36	0.21	0.261	47	-0.11	0.482	47	-0.15	0.350
Genioglossus	36	-0.18	0.334	36	-0.18	0.320	47	0.08	0.608	47	-0.01	0.956
Other Tongue	36	-0.02	0.914	36	-0.02	0.932	47	0.01	0.927	47	-0.11	0.473
Tongue Fat	31	0.22	0.260	31	0.36	0.070	**36**	**0.59**	**0.0004**	36	0.23	0.206
Total Tongue	36	-0.12	0.520	36	-0.13	0.493	47	0.11	0.503	47	-0.07	0.654
Epiglottis	35	-0.00	0.987	35	0.01	0.955	47	0.02	0.878	47	0.19	0.233
Fat Pads	35	-0.24	0.197	35	-0.26	0.160	47	0.20	0.194	47	0.07	0.668
Pterygoid	36	-0.06	0.734	36	0.00	0.980	47	0.10	0.514	47	-0.11	0.483
RP Lateral Walls	36	0.04	0.813	36	0.08	0.653	47	0.28	0.071	47	0.15	0.358
RG Lateral Walls	36	-0.01	0.939	36	0.00	0.982	47	0.01	0.968	47	-0.21	0.186
Total Lateral Walls	36	0.02	0.919	36	0.08	0.687	47	0.18	0.251	47	-0.07	0.669

†Analyses restricted to subsets of patients with specific positional AHI ≥ 5 events/hour at baseline; ‡Partial Pearson's correlation adjusted for age, gender, race and height; §Partial Pearson's correlation adjusted for age, gender, race, height and percent change in weight. Significant values after Hochberg correction shown in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

Table E6C: Partial Pearson's Correlations between Percent Change in Positional AHI and Percent Change in Abdominal Fat Measures among Patients with OSA

Abdominal Fat Volume	Supine AHI						Non-Supine AHI					
	Covariates Only			Covariates and Weight Change			Covariates Only			Covariates and Weight Change		
	N	**rho‡**	**p**	**N**	**rho§**	**p**	**N**	**rho‡**	**p**	**N**	**rho§**	**p**
Abdominal Total Fat	25	0.38	0.090	25	-0.02	0.946	39	0.37	0.031	39	-0.03	0.874
Abdominal Subcutaneous Fat	25	0.34	0.132	25	0.02	0.939	39	0.36	0.032	39	0.00	0.988
Abdominal Visceral Fat	25	0.39	0.077	25	-0.14	0.566	39	0.29	0.089	39	-0.09	0.595

†Analyses restricted to subsets of patients with specific positional AHI ≥ 5 events/hour at baseline; ‡Partial Pearson's correlation adjusted for age, gender, race and height; §Partial Pearson's correlation adjusted for age, gender, race, height and percent change in weight. Significant values after Hochberg correction shown in **bold**. Abbreviations: RP = retropalatal; RG = retroglossal

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