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Clinical, Anthropometric and Upper Airway Anatomic Characteristics of Obese Patients with Obstructive Sleep Apnea Syndrome

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Key Words
Magnetic resonance imaging · Obstructive sleep apnea · Obesity · Sleep

Abstract
Background: Obese subjects are at increased risk of developing obstructive sleep apnea syndrome (OSAS). However, the individual role of local (i.e., upper airway-related) and general (clinical and whole-body anthropometric) characteristics in determining OSAS in obese patients is still controversial. ***Objectives:*** To contrast the clinical, anthropometric and upper airway anatomical features of obese subjects presenting or not presenting with OSAS. ***Methods:*** Thirty-seven obese (BMI $\geq$30 kg/m^2) males with OSAS and 14 age- and gender-matched obese controls underwent clinical and anthropometric (BMI, waist-to-hip ratio and neck circumference) evaluation. In a subgroup of subjects (18 and 11 subjects, respectively), magnetic resonance imaging (MRI) during wakefulness was used to study the upper airway anatomy. ***Results:*** OSAS patients showed significantly higher BMI, waist-to-hip ratio and neck circumference as compared to controls ($p < 0.05$). They also referred to nonrepairing sleep, impaired attention, and previous car accidents more frequently ($p < 0.05$). The transversal diameter of the airways (TDAW) at the retroglossal level by MRI was found to be an independent predictor of the presence and severity of OSAS ($p < 0.05$). Parapharyngeal fat increase, however, was not related to OSAS. A TDAW >12 mm was especially useful to rule out severe OSAS (apnea-hypopnea index >30, negative predictive value = 88.9%, likelihood ratio for a negative test result = 0.19). ***Conclusions:*** MRI of the upper airway can be used in association with clinical and anthropometric data to identify obese males at increased risk of OSAS.

Introduction

Obesity is a well-recognized risk factor for sleep-disordered breathing [1, 2]. Although the precise mechanisms underlying this relationship are still unknown, it is generally accepted that middle-aged men with increased body mass index (BMI) presenting with large neck girth and high waist-to-hip circumference are especially predisposed to develop these abnormalities [3–7]. In particular, they are at increased risk of obstructive sleep apnea syndrome (OSAS) and its harmful cardiovascular consequences [8–12].

The anatomic abnormalities of the upper airways have been emphasized as important etiological factors for OSAS, partially due to a more reliable identification of these alterations by magnetic resonance imaging (MRI) [5, 13–17]. In this context, it has been shown that the pharynx of OSAS patients tends to present with lateral narrowing and, as a consequence, the major axis is abnormally

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oriented in the anterior-posterior dimension – a feature that could increase the airways collapsibility [11, 12, 14, 15, 18]. However, there are some controversial aspects in relation to the specific determinants of these abnormalities, especially in obese patients. For instance, some authors have demonstrated that the pattern and amount of local fat deposition are closely related to OSAS [4, 13, 19, 20]; conversely, others have found that parapharyngeal muscle hypertrophy and/or enlargement of the nonadipose soft tissues are more frequent in OSAS patients than controls [15–18]. These discrepancies may be related to the comparison between obese versus nonobese subjects in these previous studies, i.e. relatively few studies [13, 21] have addressed these aspects within the obese group.

This study, therefore, aimed to comparatively evaluate the clinical, anthropometric and upper airway anatomical features (as determined by MRI) of obese subjects with and without OSAS. In particular, we hypothesized that obese subjects with OSAS would present with distinguishable upper airway anatomical characteristics as compared to their counterparts, allowing a better characterization of the obese at increased risk of OSAS.

Patients and Methods

Subjects

Thirty-seven obese (BMI $\geq$30 kg/m^2) males with OSAS (aged 26–70 years) and 14 age- and gender-matched obese controls (males, aged 34–69) were analyzed. In the present study, an apnea/hypopnea index (AHI) $\geq$10 and a daytime sleepiness score (Epworth Sleepiness Scale) $\geq$10 were considered as indicative of OSAS. Although fewer events/hour [5] have also been considered for the definition of OSAS (associated with other clinical criteria) [22], we used a higher cutoff (AHI >10) in order to enhance the specificity of the diagnosis in these mostly middle-aged obese subjects. Patients were prospectively recruited from two tertiary centers specialized in sleep medicine: they had attended the outpatient clinic with symptoms suggestive of OSAS. Patients under treatment for OSAS, those presenting with hypothyroidism, acromegaly or a history of any surgical procedure in the upper airways were excluded from the study. No patient had a concomitant disease which could potentially affect sleep.

The controls were healthy obese subjects who were prospectively recruited from the general population or from an outpatient obesity clinic. They were required to present with a BMI $\geq$30 kg/m^2, AHI <10 and Epworth Sleepiness Scale <10 and no history of upper airway surgery. The study protocol was submitted and approved by the Institutional Medical Ethics Committee and the patients and controls gave written informed consent.

Clinical Evaluation

All subjects answered a standardized questionnaire including sleep-related symptoms, daytime hypersomnolence (Epworth Sleepiness Scale) [23], and a clinical interview including questions regarding sleepiness-related events (such as car accidents), evidence of sleep deprivation (morning headaches and nervousness), presence of sexual and/or emotional disturbances, and presence of comorbid upper airway and cardiovascular conditions.

Anthropometry

Body height (cm) was measured with the subjects standing barefoot and was determined to the nearest 0.5 cm. Total body mass (kg) was measured with subjects in light clothing and was established to the nearest 0.1 kg. From these measurements, BMI was calculated (weight/height^2, kg/m^2). The circumference of the abdominal wall at the end-expiratory level (at the mid-level between the last rib and the iliac crest) was expressed in relation to hip circumference (major trochanter) with subjects in the standing position (waist-to-hip circumference ratio). The neck circumference (cm) was measured with the subject in the standing position at the level of the cricothyroid cartilage.

Polysomnography

One-night polysomnography was performed in a sleep laboratory using a 16-channel digital polygraph (Healthdyne Alice 3, Marietta, Ga., USA). Sleep (and its various stages) was recorded and classified by standard electroencephalographic, electro-oculographic and electromyographic (genioglossus and anterior tibial) criteria [22, 24]. Cardiac rhythm and heart rate were continuously monitored through a single-lead electrocardiogram and the chest wall-abdominal movements were determined by a dual-channel displacement plethysmography. Oxyhemoglobin saturation was monitored by pulse oximetry. Apnea was defined as the cessation of the airflow at the nose and mouth (thermistors) for longer than 10 s. Hypopnea was established by the presence of at least 50% reduction in airflow for 10 s with a >4% fall in oxygen saturation and/or an arousal [22].

Upper Airway MRI

Participants were examined fully awake (without sedation) at the Sleep Institute (Federal University of São Paulo, Brazil) and at the Bio-Imagem Diagnostic Imaging Service in Salvador (Bahia, Brazil) in the supine position. MRI was performed with two 1.5-tesla superconducting magnets (Philips® Intera in São Paulo and Siemens® Synphony in Salvador). The same protocol for imaging acquisition and interpretation was applied in the two centers. The sequences were acquired as follows: (1) axial spin-echo T1-pondered (19–23 images); FOV (field of view) 230 mm; matrix 256 × 256; 6-mm thickness every 0.6 mm; time repetition (TR) 668 ms; time of echo (TE) 15 ms; number of excitations (NEX) 2; (2) sagittal 3D, fast field echo (120 images); FOV 230 mm; matrix 256 × 256; 1-mm thickness; TR 25 ms; TE 4.6 ms; flip angle 30°, and (3) axial T2 turbo spin echo (19–23 images); FOV 230 mm; matrix 256 × 256; 6-mm thickness every 0.6 mm; TR 3,058 ms; TE 80 ms; NEX 3.

A single MRI-trained radiologist (SKK) measured the airways and soft tissue structure dimension after a previous selection of the most appropriate images. A workstation with image processing software (Philips EasyVision®, The Netherlands) was used for MRI measurements: all linear measurements were expressed in millimeters. The transversal and the anterior-posterior diameters of the airways at the retroglossal level (TDAW and APDAW) were determined at the axial dimension of lowest caliber: from the

product of these diameters, the area of the airways lumen was calculated (mm^2). Bilateral muscular pharyngeal thickness was defined by the distance between parapharyngeal fat pads and the air column (fig. 1). The thickness of the parapharyngeal fat pads at the retroglossal level was also calculated. Other measurements included: the palatal-epiglottal distance, the anterior-posterior lingual diameter, the palatal-posterior wall diameter, and the epiglottal-posterior wall diameter [25, 26]. The anterior and posterior angles (°) between the lower mandible (M), hyoid bone (H) and the second cervical vertebra (C2) were also calculated (AMHC2 and PMHC2 angles, respectively) (fig. 2).

Data Analysis

Statistical calculations were performed with the statistics software package SPSS for Windows 13.0 (SPSS, Chicago, Ill., USA). Continuous data are expressed as mean and standard deviations (SD) and the frequency of categorical variables are expressed in proportions. Nonpaired Student's t test were used to compare the responses between patients and controls. The level of association between categorical variables was determined by using Pearson's χ^2 or Fisher's exact test when appropriate. Pearson's product-moment correlation coefficient was used to assess the degree of linear correlation between continuous variables. In the subgroup of patients who were submitted to MRI, logistic regression analysis was used to determine the independent predictors of OSAS and a backward stepwise multiple regression analysis was used to define the determinants of OSAS severity (as estimated by the AHI). The probability of a type I error was established at 5% for all tests ($p < 0.05$).

Results

Clinical and Anthropometric Characteristics

The main clinical and anthropometric characteristics of both groups are shown in table 1. Obese subjects with OSAS showed significantly higher BMI, waist-to-hip ratio and neck circumference as compared to controls ($p < 0.05$). As expected, nonrepairing sleep, impaired attention, previous car accidents and sleep apnea seen by the spouse were all significantly more frequent in the patient group than in controls ($p < 0.05$).

Polysomnography

As expected from the criteria for group definition, the AHI was significantly higher in patients than controls ($p < 0.05$). Additionally, OSAS patients presented with lower resting and sleep-related oxyhemoglobin desaturation. Sleep efficiency and the duration of REM sleep were also significantly more impaired in patients as compared to controls (table 1).

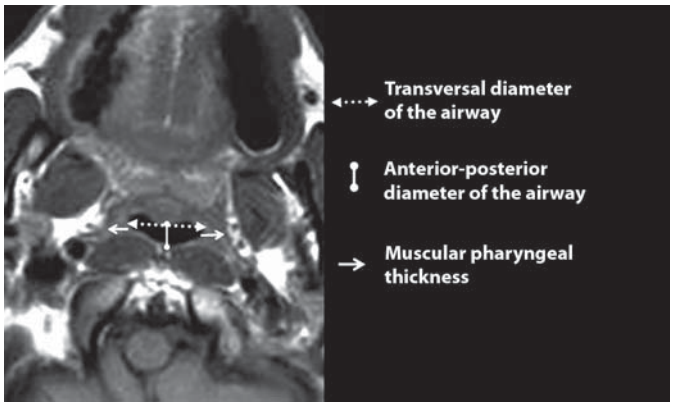

Fig. 1. Axial T1-weighted spin-echo MRI of the velopharynx in a representative subject. Note that the parapharyngeal muscular thickness corresponds to the distance between the fat pads and the airway.

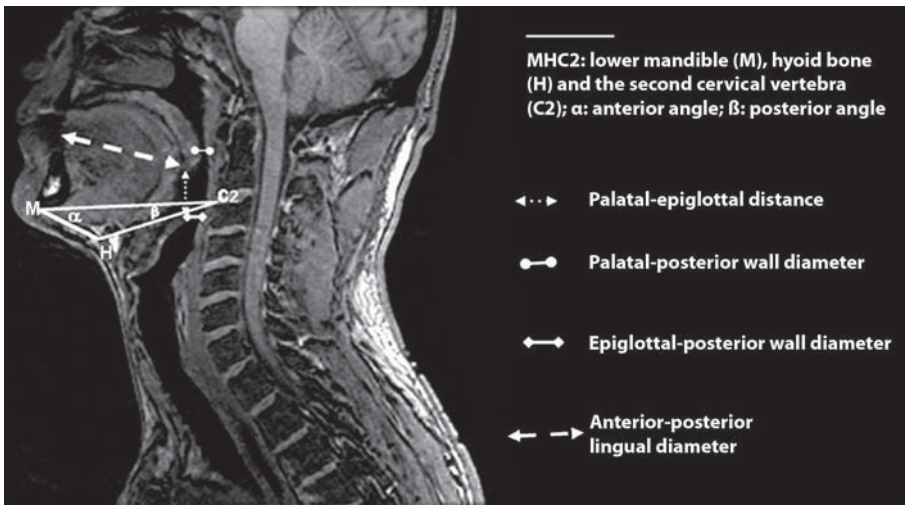

Fig. 2. Sagittal T1-weighted spin-echo MRI of the upper airways in a representative subject.

Table 1. Characteristics of the study population

	Controls (n = 14)	OSAS (n = 37)
Demographic/anthropometric		
Age, years	50.0 ± 10.2	47.9 ± 9.6
BMI, kg/m^2	31.5 ± 2.7	35.5 ± 4.7*
Waist-to-hip ratio	1.0 ± 0.1	1.2 ± 0.2*
Neck circumference, cm	43.2 ± 2.5	45.4 ± 3.2*
Clinical, number of subjects		
Night awakenings, >3 times/night	13/14 (92.9%)	36/37 (97.3%)
Snoring, >3 times/week	14/14 (100%)	37/37 (100%)
Apnea seen by the spouse	9/14 (64. 3%)	35/37 (94.6%)*
Morning headaches	4/14 (28.6%)	22/37 (59.5%)
Nonrepairing sleep	7/14 (50%)	31/37 (83.8%)*
Car accidents	1/14 (7.1%)	17/37 (45.9%)*
Nervousness	9/14 (64.3%)	28/37 (75.7%)
Impaired attention	9/14 (64.3%)	34/37 (91.9%)*
Impairment of sexual performance	3/14 (21.4%)	14/37 (37.8%)
Polysomnographic		
AHI, events/hour sleep	6.0 ± 2.7	44.2 ± 20.2*
Sleep efficiency, %	85.9 ± 6.4	80.8 ± 8.5*
Sleep III and IV, %	14.6 ± 8.0	12.1 ± 8.3
REM sleep, %	16.0 ± 9.6	8.9 ± 6.9*
SpO_2 baseline, %	94.6 ± 1.5	92.7 ± 2.3*
SpO_2 nadir, %	82.6 ± 7.7	69.4 ± 14.8*

* $p < 0.05$. REM = Rapid eye movement; SpO_2 = oxyhemoglobin saturation by pulse oximetry.

Table 2. Upper airway anatomical characteristics according to MRI in obese subjects presenting or not presenting with OSAS

	Controls (n = 11)	OSAS (n = 18)
AMHC2, degrees	29.2 ± 7.0	32.2 ± 8.0
PMHC2, degrees	26.9 ± 7.9	30.6 ± 8.2
Palatal-epiglottal distance, mm	22.6 ± 6.6	22.4 ± 8.6
Airway anterior-posterior diameter, mm	5.2 ± 2.9	6.2 ± 6.0
Airway transversal diameter, mm	13.7 ± 6.1	9.3 ± 4.1*
Total upper airways area, mm^2	72.2 ± 71.0	69.5 ± 115.7
Pharyngeal muscular thickness, mm	20.3 ± 8.7	25.2 ± 7.5***
Parapharyngeal fat pad thickness, mm	19.6 ± 8.7	18.7 ± 9.7
Anterior-posterior lingual diameter, mm	66.3 ± 7.6	67.8 ± 7.7
Palatal-posterior wall diameter, mm	3.7 ± 1.9	3.8 ± 2.8
Epiglottal-posterior wall diameter, mm	6.9 ± 2.1	10.3 ± 6.0**

* $p < 0.05$; ** $p = 0.08$; *** $p = 0.13$. AMHC2 and PMHC2 = Anterior and posterior angles between the lower mandible (M), hyoid bone (H) and the second cervical vertebra (C2).

MRI Data

The MRI analysis of the upper airways showed some important differences between the groups. Although the total area of the upper airways did not differ between the groups, there were significant differences in the shape of the airways. Therefore, OSAS patients presented with evidence of reduced laterolateral dimension (lower transversal diameter of the airways, TDAW) and increased anterior-posterior axis (table 2, fig. 3). This lateral narrowing tended to be associated with increased muscular

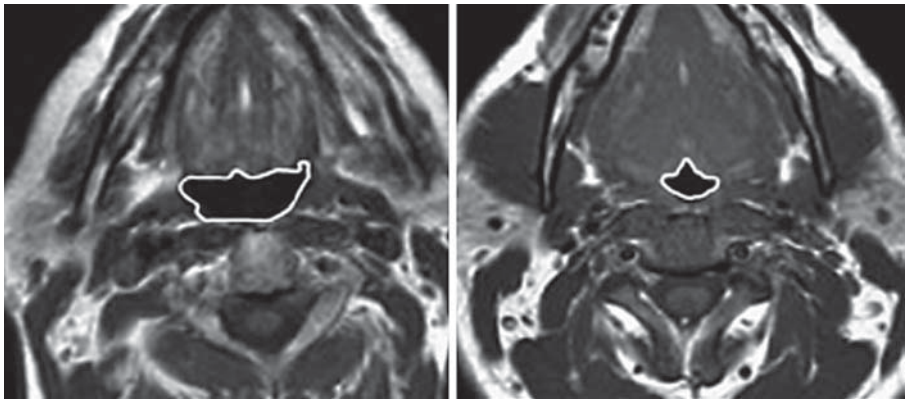

Fig. 3. Axial T1-weighted spin-echo images of the pharynx at the retroglossal level in an obese control (left) and a patient with OSAS (right): note the increase in the anterior-posterior diameter with evidence of lateral narrowing (reduction of transversal diameter of pharynx air column) in the patient with OSAS.

Table 3. Final logistic regression model for the prediction of OSAS in obese subjects

	B	SE	Wald	p	OR
Airway transversal diameter, mm	–0.223	0.134	2.756	0.09	0.80
SpO_2 nadir	–0.221	0.095	5.426	0.02	0.80
Constant	20.0	8.31	5.783	0.01	

Variables considered in the initial model: airway transversal diameter; epiglottal-posterior wall diameter; waist-to-hip ratio; neck circumference; SpO_2 nadir. B = Logistic coefficient; SE = standard error; OR = odds ratio; SpO_2 = oxyhemoglobin saturation by pulse oximetry.

Table 4. Final model of a multiple regression analysis for the prediction of OSAS severity (AHI) in obese subjects

	B	SE	t	p
AMHC2, degrees	0.931	0.476	1.955	0.06
Airway transversal diameter, mm	–1.515	0.732	–2.069	0.04
Constant	12.804	17.336	0.739	

Variables considered in the initial model: airway transversal diameter; epiglottal-posterior wall diameter; waist-to-hip ratio; neck circumference; SpO_2 nadir. SE = Standard error; AMHC2 = anterior angle between the lower mandible (M), hyoid bone (H) and the second cervical vertebra (C2).

thickness (p = 0.13) with no difference in the thickness of the parapharyngeal fat pads. In addition, there was a trend for both the anterior and posterior angles between the lower mandible (M), hyoid bone (H) and the second cervical vertebra (C2) (AMHC2 and PMHC2 angles, respectively) to be increased in patients as compared to controls (table 2).

In a multiple logistic regression analysis, TDAW and the nadir of SpO_2 were independently associated with OSAS (table 3). Furthermore, TDAW and the PMHC2 angle were independent predictors of OSAS severity (AHI) (table 4). In fact, a TDAW >12 mm was especially useful to rule out a severe obstructive sleep apnea/hypopnea syndrome (OSAHS; AHI >30: negative predictive value = 88.9 %, likelihood ratio for a negative test result = 0.19) (fig. 4).

Discussion

The results of the present investigation indicate that clinical, anthropometric and MRI data can be used in association to identify obese males at increased risk of OSAS. The main results of this study can be summarized as follows: (1) OSAS patients showed significantly higher BMI, waist-to-hip ratio and neck circumference as compared to controls; (2) a smaller TDAW by MRI was an independent predictor of presence and severity of OSAS, being especially useful to rule out severe OSAS (AHI

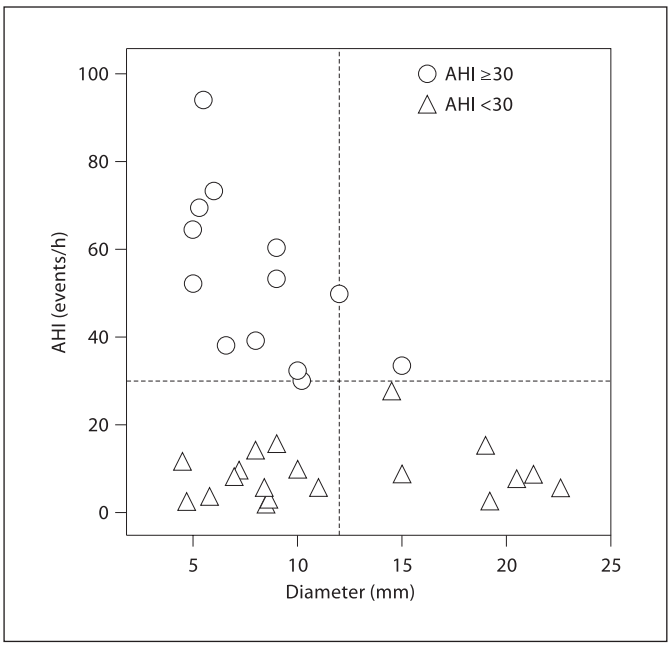

Fig. 4. Scatterplot of the relationship between the TDAW and the severity of OSAS in obese males: a TDAW >12 mm was particularly useful to exclude severe OSAS (AHI >30/h, $p < 0.05$).

>30/h), and importantly (3) a lateral narrowing of the airway was not associated with increased fat pad thickness.

There are a number of hypotheses that could explain the link between excess weight and OSAS, including (1) upper airway abnormalities in structure (e.g. geometry and pattern of nonadipose soft tissue deposition) and/or function (increased collapsibility and changes in muscular tone), (2) alterations of chest wall compliance, and (3) intrinsic disturbances of the relationship between neural drive and elastic load compensation [11, 12, 18]. Our results showed that obese subjects with OSAS present with some distinct clinical and anthropometric characteristics when compared with their counterparts without OSAS (table 1). In particular, patients were more likely to refer to nonrepairing sleep, a history of car accidents and impaired attention. These data point out the need of an early recognition and treatment of the disorder in the obese since car accident-related events are important consequences of untreated OSAS [27, 28].

A particularly interesting feature of this study was the ability of MRI data to estimate the likelihood of OSAS, independent of clinical and anthropometric variables. Our results are in line with previously reported data which demonstrate that the upper airways at the pharyngeal level of OSAHS patients – even in the nonobese – tends to be narrower due to lateral narrowing [11, 12, 14, 15]. Therefore, the velopharynx of obese subjects without OSAS had an elliptic shape with the long axis oriented in the transversal plane. In contrast, OSAS patients tended to present with the long axis oriented in the sagittal plane (fig. 3). Importantly, however, this was not associated with increased local fat deposition (table 2); therefore, this might indicate that parapharyngeal muscular hypertrophy was a possible mechanism to explain the lateral narrowing in this population (see below). In fact, we did find a trend for increased parapharyngeal muscle mass in OSAS patients (table 2). These data, therefore, indicate that differences in the magnitude and pattern of fat deposition do not seem to explain why some obese subjects develop OSAS.

Although a number of previous investigations have contrasted the upper airway anatomy of obese versus nonobese subjects [4, 17, 19, 20], relatively few studies have looked at these aspects in obese subjects with and without OSAS [13, 21]. Based on the former studies, the prevailing concept is that fat deposition and/or fatty infiltration in the surrounding areas of the pharynx would be related to the presence and severity of OSAS [4, 19, 20, 29]. However, as cited, in the present study OSAS patients did not present with parapharyngeal fat deposition; by exclusion therefore, local muscle hypertrophy seems to be a natural candidate for the lateral narrowing (table 2). Our data are in line with those of Ciscar et al. [16] who also found that the reduction on the transversal diameter of the airways was more associated with muscle hypertrophy than fat deposition. Schwab et al. [15, 17] also found that enlargement of the nonadipose soft tissue structures were associated with OSAS: the authors conclude that differences in the size of upper airway structures between patients and controls could not simply be explained by fat deposition at this level.

In this context, Petrof et al. [30, 31] advanced the concept that chronic load and altered pattern of usage imposed on the upper airway dilators in OSAS lead to myopathic changes that may ultimately impair the ability of these muscles to maintain pharyngeal patency. In fact, other authors have shown that the parapharyngeal muscles of OSAS patients may present with increased neural activation [32] and impaired electromyographic responses to intraluminal negative pressures [33]. In addition, nonoxidative, force-generating type IIb fibers have been shown to be present at parapharyngeal muscles in a higher percentage in OSAS patients as compared to controls

[34]. However, it should be pointed out that the differences in parapharyngeal muscle mass did not reach statistical significance in the present study; further studies, therefore, are warranted to evaluate this issue in well-matched obese subjects with and without OSAS.

This study presents some limitations. First, the number of subjects who were effectively submitted to MRI was relatively small. Second, MRI was not performed during sleep and some abnormalities could have been missed by the isolated analysis of awake subjects. However, it is conceivable that the abnormalities found in the awake condition are likely to be present in the sleeping subject. Third, it is not known whether our results are also applicable to a population with more severe disease, especially those patients with a worse health status. In addition, the issues of interobserver variability of the MRI data, the effects of comorbid conditions on the anatomical abnormalities and the dynamic analysis of the pharyngeal wall compressibility were not addressed in the present study. More importantly, the groups were not well-matched in relation to weight (table 1); we simply cannot rule out that the MRI abnormalities in the OSAS group were due to a higher degree of obesity in these patients. However, even considering that OSAS patients were more obese than the controls, they did not present with more parapharyngeal fat, which is consistent with the notion that fat deposition is not a major factor to explain airway narrowing in obese subjects with OSAS.

In conclusion, MRI of the airway might provide clinically useful information to identify obese males at increased risk of OSAS – especially if MRI data are associated with clinical and anthropometric characteristics. These results point out that upper airway anatomy has an effect on the etiology of OSAS in this patient population.

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