Morphologic Analyses of Mandible and Upper Airway Soft Tissue by MRI of Patients With Obstructive Sleep Apnea Hypopnea Syndrome

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Study Objectives: To evaluate the morphological features of the mandible and the volume of the upper airway soft tissues in determining the anatomical risk factors for the upper airway in Japanese male patients with obstructive sleep apnea hypopnea syndrome (OSAHS).

Methods: Five morphological parameters of the mandible at the mandibular base plane and three volumetric parameters of the upper airway soft tissue were analyzed using three-dimensional (3D) magnetic resonance imaging software in 31 OSAHS and 20 controls.

Results: There were no significant differences between the two groups in mandibular internal width (the distance between the internal right and left gonia [IRG and ILG]) and mandibular bony thickness. However, the patients with OSAHS had a significantly wider mandibular divergence (the angle between the spina mentalis (SM)- IRG line and SM- ILG line), a smaller mandibular internal length (the perpendicular distance from SM to the RG- LG line), and a smaller area than the normal subjects at the mandibular base plane. There were no significant differences in these morphological parameters for the mandible between obese and nonobese OSAHS patients. The volumes of the tongue, soft palate, and lateral pharyngeal walls were not significantly different between the OSAHS and the control groups.

Conclusions: Japanese male OSAHS patients had specific anatomical features in the bottom part of the mandible; however, obesity seemed to be a less significant risk factor. Investigators and clinicians must realize that ethnicity may modify the effects of obesity and abnormal craniofacial anatomy as risk factors for the pathogenesis of OSAHS.

Keywords: Obstructive sleep apnoea, 3D MRI, Japanese, mandible, tongue volume, soft palate volume, lateral pharyngeal wall

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INTRODUCTION

OBSTRUCTIVE SLEEP APNEA HYPOPNEA SYNDROME (OSAHS) IS CHARACTERIZED BY A REPETITIVE OBSTRUCTION OF THE UPPER AIRWAY DURING sleep. Increasing respiratory effort against an obstructed upper airway leads to recurrent cessations of airflow associated with transient episodes of oxygen desaturation and hypercapnia, and arousal produced by the respiratory effort induces upper airway muscle tonus activity and apnea termination coincident with postapneic hyperventilation.[1] Pharyngeal airway size is determined by the interaction between the neural regulation of pharyngeal airway dilator muscle activity and the structural properties of the pharyngeal airway.[2] Pharyngeal collapse during sleep in patients with OSAHS may be caused by structural abnormalities of the pharyngeal airway and impairment in the neural regulation of pharyngeal muscle activity.[3]

Disclosure Statement

This was not an industry supported study. Drs. Suzuki, Okubo, Horiuchi, Okabe, Ikeda, Higano, Mitani, Hida, Kobayashi, and Sugawara have indicated no financial conflicts of interest.

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The primary structural risk factors for OSAHS are either obesity or having an abnormal upper-airway anatomy. Obesity increases the size of the soft-tissue structures in the upper airway, which decreases the size of the upper airway.[4] Certain craniofacial structures have also been shown to predispose patients to OSAHS. Craniofacial morphologies determined by cephalometric analyses have been reported to be strongly associated with the development of OSAHS. Tendencies toward retrognathia, micrognathia, long face, and inferior positioning of the hyoid bone in patients with OSAHS are characteristic features that have been widely noted.[5,10] In addition, tendencies toward a decreased cranial base length and angle, a steep mandibular plane, elongated maxillary and mandibular teeth, a narrow upper airway, a long and large soft palate, and a large tongue have also been indicated.[6-12] However, these early reports were limited to the analyses of data obtained from sagittal views. Recent studies have demonstrated that 3-dimensional (3D) magnetic resonance imaging (MRI) techniques performed during wakefulness are suitable for the evaluation of upper airway volume in patients with OSAHS.[4,13-15] Volumetric analysis of the upper airway by 3D MRI during wakefulness was used in a case-control study of patients with and without OSAHS. It revealed that the soft-tissue volumes of the retropalatal and retroglossal lateral pharyngeal walls, soft palate, tongue, and genioglossus muscle are significantly larger in patients with OSAHS, indicating that OSAHS is exacerbated by larger volumes of almost all soft-tissue structures in Caucasians.[4,13] On the other hand, Asian men tend to be less obese but have more severe OSAHS than do Caucasian men, controlled for age and body mass index (BMI). Moreover, there are differences in craniofacial charac-

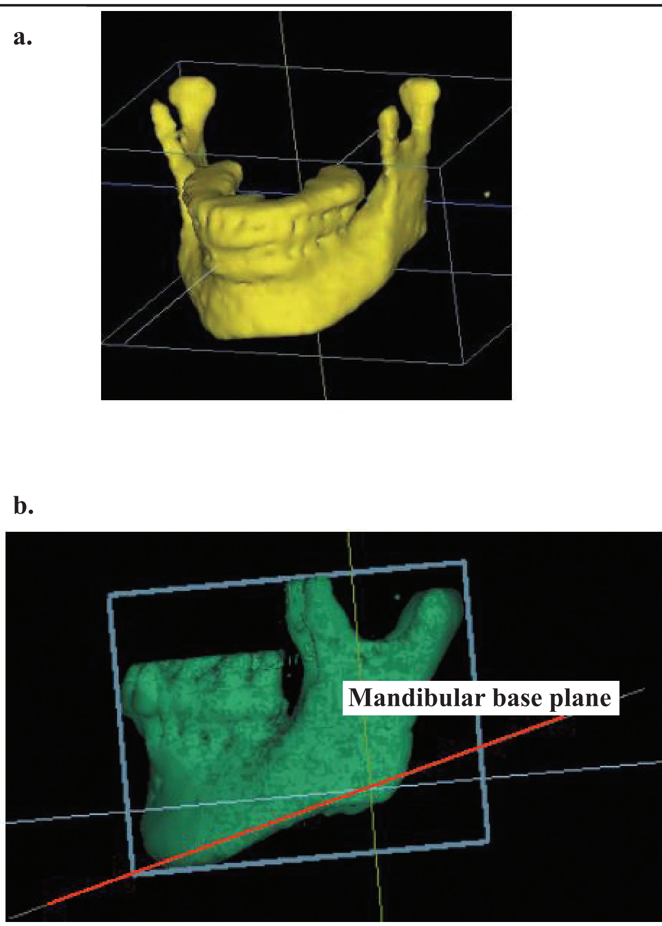

Figure 1a—Three-dimensional volumetric magnetic resonance imaging reconstruction of mandible; **b,** Level of mandibular base plane.

teristics, which pose as risk factors, such as significantly smaller maxillae and mandibles, increased total and upper facial heights, and steeper and shorter anterior cranial bases in Asian men.[16, 17] However, studies on axial and 3-D craniofacial morphologies of patients with OSAHS among the Asian population have not yet been reported.

In this study, the morphologic characteristics of the mandible and upper airway soft tissue were elucidated using 3D volumetric MRI reconstruction to clarify the anatomic risk factors for the upper airway in Japanese patients with OSAHS.

PATIENTS AND METHODS

Subjects and Polysomnography

The study population consisted of 51 Japanese men, (31 patients with OSAHS and 20 healthy control subjects). Data were collected from August 2001 to July 2002. All the patients were newly diagnosed as having OSAHS. Patients with OSAHS were excluded when there was evidence of enlarged tonsils or predominant central sleep apnea on polysomnography (PSG). None of the patients with OSAHS had been treated surgically or by any other methods for sleep apnea. Patients with irregular sleep-wake schedules and periods of sleep deprivation, such as shift workers, were excluded from this study. MRI studies of patients with OSAHS were performed before the beginning of treatment with continuous positive airway pressure. None of the control subjects had a history of snoring or excessive daytime sleepiness. The obese subjects were stratified according to the criteria of the Japanese Society for the Study of Obesity; nonobesity was defined as having a BMI < 25 and obesity as having a BMI of 25 kg/m^2 or higher.[18, 19] The Institutional Review Board of our institute approved the study after review by the ethics committee, and informed consent was obtained from all the subjects.

Overnight PSG were recorded in all the OSAHS subjects. For digital PSG, the following examinations were carried out: electroencephalography (C4/A1, and C3/A2), electrooculography, submental electromyography, and electrocardiography using surface electrodes, the airflow at the nose and mouth using thermistors, the respiratory movements of the rib cage and abdomen by inductive plethysmography, and percutaneous arterial oxygen saturation using a finger pulse oximeter. The predominant sleep stage was determined according to the criteria established by Rechtschaffen and Kales.[20] Arousal responses were identified according to the criteria of the American Sleep Disorders Association.[21] Potential apnea was identified as a nearly flat airflow (< 10 % of baseline) and hypopnea as an airflow < 95 % of the baseline for at least 10 seconds associated with either an oxygen desaturation of > 3 % or an arousal.

Analyses of Mandibular Morphology by 3-D Volumetric MRI Reconstruction

MRI was performed on patients with OSAHS and control subjects using a Signa Horizon LX1.5T CVi (G.E. USA) with a quadrature head coil. Axial-plane sections were obtained by T1-weighted MRI using Fast SPGR 3D (TR/TE/FA, 8.9 /4.2 /8.0 ms, FOV, 220 × 220 mm; Matrix, 256 × 224). Sixty-four 2-mm-thick slices were each obtained from the hard palate to the epiglottic vallecula, the base of the epiglottis. The axial section was imaged parallel to a raised baseline (the line on both the Sella turcica and the fourth cerebral ventricle. During axial MRI, all subjects were in the supine position with their heads placed in a neutral position to ensure consistent positioning. Each subject was examined during wake and tidal breathing for almost 4 minutes and 15 seconds. Fast SPGR 3D was chosen as the photography condition of MRI because this method can produce thin imaging sections and has a high spatial resolution, high signal-to-noise ratio, and the capability to reconstruct a desired plane.[22-24] Using 3D imaging software V-works (Cybermed Inc., Seoul, Korea), the mandible was trimmed for each slice from the bottom to the head. The mandible was carefully outlined, and its internal structure was smeared. Then, it was rotated 360º, after which its smoothness on the surface was checked and inaccurate parts were corrected. These procedures were repeated until smooth 3D structures of the mandible were obtained (Figure 1a).

To test the precision of the reconstructed mandibles by 3D MRI methods, computed tomography (CT) scans were taken, and the mandibles of 3 control subjects were reconstructed using V-works. In addition, comparison studies were performed between direct measurement and the 3D MRI reconstruction of the mandible volume using the rapid prototyping model of the mandible (n = 3). The volume of the rapid prototyping model of the mandible was directly measured by the water titration method. Then, the rapid prototyping model of the mandible was placed in a Gadteridol solution, an MRI contrast medium that allows the rapid prototyping model to be visible on MRI scans and to be able to obtain the reconstructed 3D structures of the mandible.

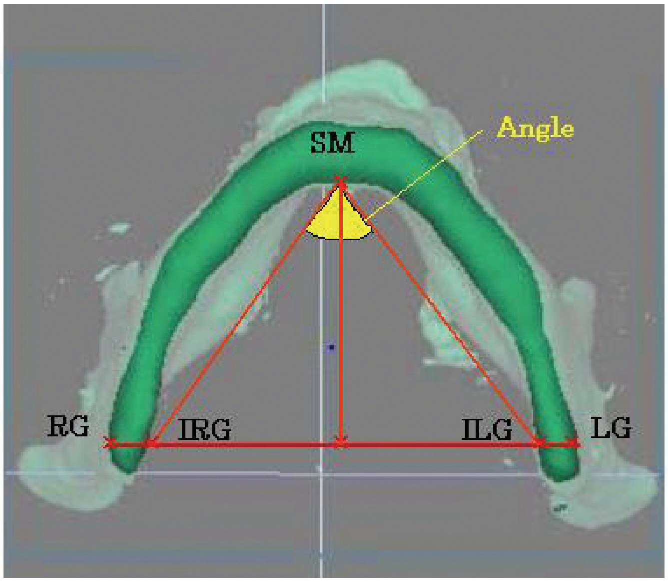

Figure 2a—Axial morphologic analyses of mandible on mandibular base plane. LG refers to left gonion; ILG, internal left gonion; RG, right gonion; IRG, internal right gonion; SM, spina mentalis; Angle, mandibular divergence, degree between SM-IRG line and SM-ILG line. The mandibular internal width was determined from the distance between IRG and ILG. Mean distances between RG and IRG and between LG and ILG were defined as the mandibular bony thickness. The mandibular internal length was determined from the perpendicular distance from the spina mentalis to the line on both RG and LG.

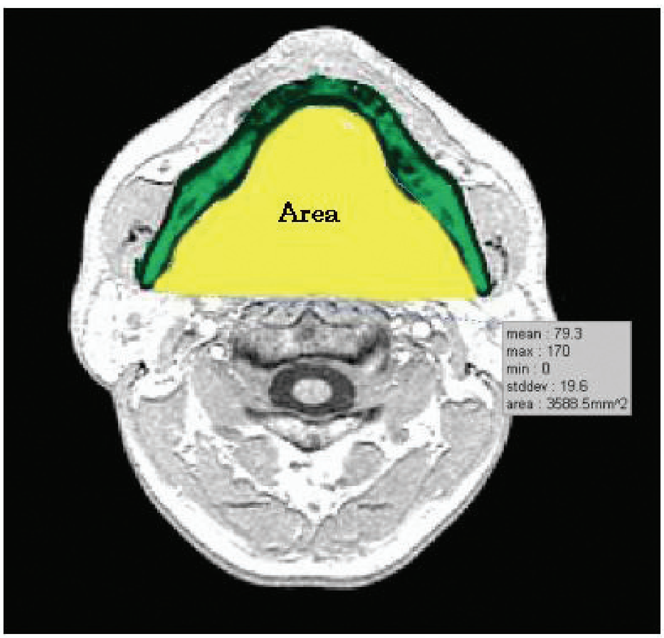

Figure 2b—Area, integration of area within internal mandible.

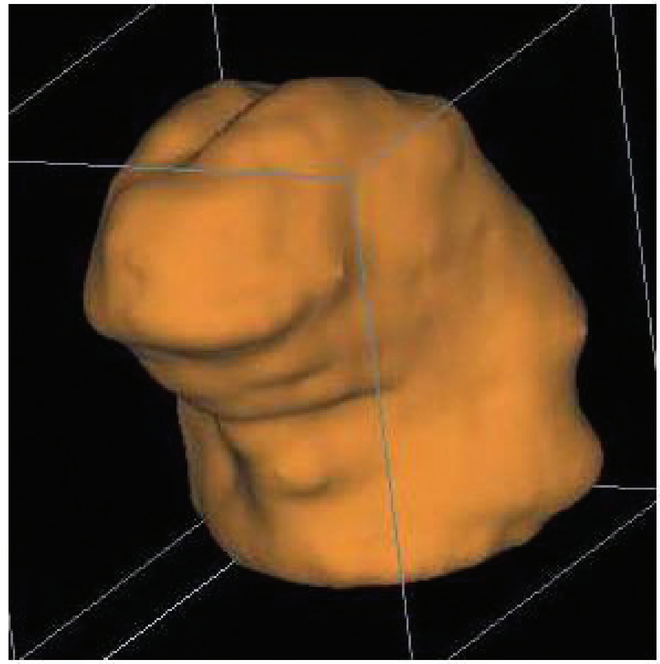

Figure 3a—3-Dimensional volumetric magnetic resonance imaging reconstruction of the tongue.

Mandibular and Soft-Tissue Parameters

Five measurements of the mandible and 3 measurements of soft tissues were analyzed using 3D imaging software. The 3D structures of the mandible were moved and rotated on the computer to detect the section in which the entire bottom of the corps mandibulae was revealed. This plane was defined as the mandibular base plane in this study (Figure 1b). We performed the axial morphologic analyses of the mandible at the following 3 planes; the mandibular base plane, the plane parallel to the mandibular base plane connecting the tip of the mandibular central incisors (mandibular occlusal plane), and the plane at the middle between the 2 planes (middle plane). Figures 2a and b schematically show the results of the axial morphologic analyses of the mandible on the mandibular base plane. The gonion was defined as the most external protrusive point of the angulus mandibulae. The internal gonion was defined as the intersecting point on the internal surface of the angulus mandibulae that connected the line on both the right gonion (RG) and the left gonion (LG). The mandibular internal width was determined from the distance between the internal right gonion (IRG) and the internal left gonion (ILG). The mean distances between RG and IRG and between LG and ILG were defined as the mandibular bony thickness. The mandibular divergence was defined as the degree between the spina mentalis (SM)-IRG line and the SM-ILG line. The mandibular internal length was determined as the perpendicular distance from the spina mentalis to the line on both RG and LG (Figure 2a). The integration of the area within the internal mandible, hereafter referred to as the area, was digitally calculated on the lowest slice in which the entire corpus mandibulae appeared (Figure 2b).

The tongue, soft palate, and lateral pharyngeal walls were trimmed in each slice using 3D imaging software from the bottom to the head of each anatomic structure. The tongue and soft palate were carefully outlined, and the inside of the tongue and soft palate were smeared on each of the axial and sagittal planes (Figures 3a, b, and c). The lower edge of the tongue was extracted to the bottom edge of the mandible. The measuring method of the lateral pharyngeal wall was according to Dr. Schwab's method.[15]

Statistical Analyses

All descriptive statistics are presented as mean ± SD. Descriptive statistics were calculated for each variable. Unpaired and paired subjects were evaluated by the Mann-Whitney U-test and Wilcoxon t-test, respectively. Correlations between parameters were analyzed using the Spearman correlation coefficient test. All p value tests were 2-tailed. A p value of less than .05 was

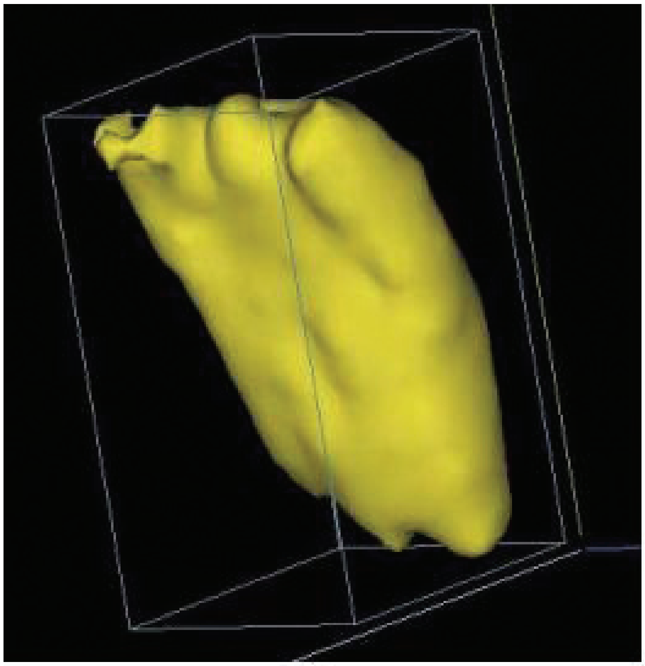

Figure 3b—3-Dimensional volumetric magnetic resonance imaging reconstruction of the soft palate.

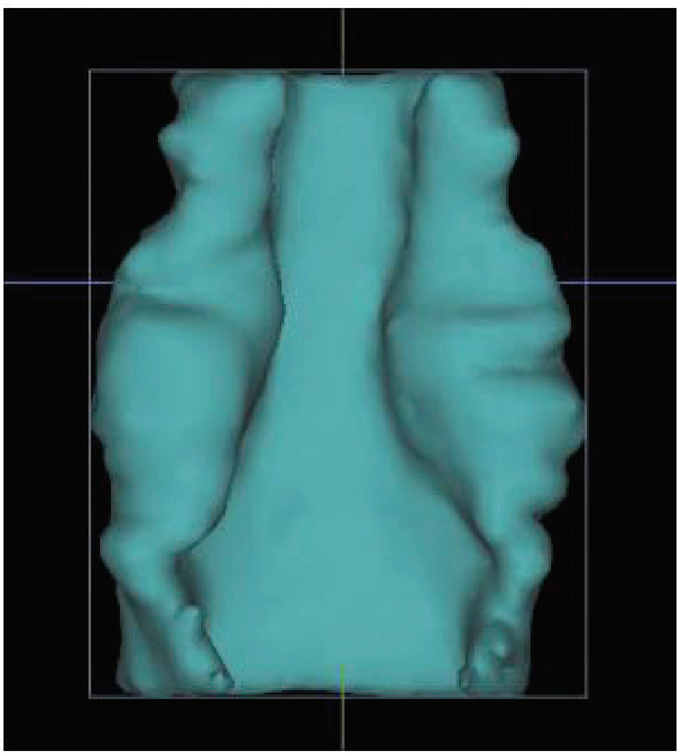

Figure 3c—3-Dimensional volumetric magnetic resonance imaging reconstruction of the lateral pharyngeal wall.

considered to indicate statistical significance. Logistic regression analysis was used to verify the possibility of variables for predicting the OSAHS using the statistical package SPSS ver.12.1 (SPSS Inc., Chicago, IL).

RESULTS

Characteristics of Patients With OSAHS and Control Subjects

The PSG of the 31 patients with OSAHS showed that they had mild to severe OSAHS with an apnea-hypopnea index (AHI) of 45.6 ± 18.6 per hour, ranging from 11.7 to 77.4 per hour. The average ages of the OSAHS and control groups were 50.8 ± 14 and 38.4 ± 10 years, ranging from 24 to 73 and 25 to 58 years, respectively. The average BMIs of the OSAHS and control groups were 25.7 ± 2.7 kg/m^2 and 24.2 ± 3.2 kg/m^2, respectively. There was a significant difference in age (p = .002) between the 2 groups but not in BMI (p = .060); (Mann-Whitney U-test).

Table 1—Comparison of 3-Dimensional Magnetic Resonance Imaging Reconstruction Parameters from Japanese Men With OSAHS and Control Subjects

Variables	OSAHS	Control	p Value
Mandibular internal width, mm	88.8±5.0	89.7±4.7	.760
Mandibular divergence,º	77.5±5.1	73.5±5.1	.010**
Mandibular bony thickness, mm	6.5±1.1	6.1±1.3	.200
Mandibular internal length, mm	53.9±4.2	57.4±5.0	.040*
Area, cm^2	32.7±4.6	37.0±4.4	.002**
Tongue volume, cm^3	78.1±11.9	77.1±11.6	.910
Soft palate volume, cm^3	6.1±2.3	5.9±1.2	.860
Lateral pharyngeal wall volume, cm^3	20.4±3.6	18.5±3.4	.060

All mandibular parameters were based on the mandibular base plane. *p < .05, **p < .01 (Mann-Whitney U-test). OSAHS, obstructive sleep apnea hypopnea syndrome

Parameter Analyses of 3D Volumetric MRI Reconstruction

The directly measured volume and calculated volume of the 3D reconstructed rapid prototyping model of the mandible were 85.13 and 79.98 (model No. 1), 99.35 and 83.81 (model No. 2), and 127.1 and 115.4 cm^3 (model No. 3). There was no significant difference between the directly measured volume and the calculated volume of the 3D reconstruction (p = .55). The comparison between the CT measurements and the MRI measurements in the 3 control subjects also revealed that there was no significant difference between the reconstructed volume of the mandibles by MRI and CT in the same subjects (p = .88). These results suggest that 3D MRI reconstruction methods are almost precise.

To evaluate the morphologic differences between the OSAHS and control groups, the mandible, tongue, soft palate, and lateral pharyngeal walls were analyzed by 3D volumetric MRI reconstruction. There was no significant difference between the 2 groups in mandibular internal width (p = .76) or mandibular bony thickness (p = .20) on the mandibular base plane. However, the patients with OSAHS had a significantly wider mandibular divergence (p = .010), a smaller mandibular internal length (p = .040), and a smaller area (p = .002) than did the control subjects on the mandibular base plane (Table 1). In contrast, there was no significant difference between the 2 groups in all 5 mandibular parameters on the mandibular occlusal or middle plane. Tongue volume (p = .91), soft palate volume (p = .86), and lateral pharyngeal wall volume (p =.06) were not significantly different between the OSAHS and control groups. The results of the 3D MRI reconstruction parameter analyses are summarized in Table 1.

To elucidate the effect of obesity on the size of the mandible and upper-airway soft-tissue structures, 3D MRI reconstruction parameters were compared between obese (n = 12) and nonobese (n = 19) patients with OSAHS. All mandibular parameters were based on the mandibular base plane. There were no significant

Table 2a—Comparisons of 3-Dimensional Magnetic Resonance Imaging Reconstruction Parameters Between Obese and Nonobese Patients

Variables	BMI ≥ 25	BMI < 25 kg/m²	p Value
Mandibular internal width, mm	88.9±5.6	88.7±4.1	.69
Mandibular divergence,°	77.8±5.2	77.1±5.3	.73
Mandibular bony thickness, mm	6.6±1.2	6.4±1.1	.65
Mandibular internal length, mm	54.0±4.9	53.7±3.0	.58
Area, cm²	33.0±5.3	34.6±8.5	.97
Tongue volume, cm³	79.1±13.2	76.4±9.7	.69
Soft palate volume, cm³	6.2±2.3	5.9±2.4	.57
Lateral pharyngeal wall volume, cm³	20.5±3.8	20.2±3.5	.81

All mandibular parameters were based on the mandibular base plane. BMI, body mass index

Table 2b—Comparisons of 3-Dimensional Magnetic Resonance Imaging Reconstruction Parameters Between Patients with Severe and Mild to Moderate Obstructive Sleep Apnea-Hypopnea Syndrome

Variables	AHI ≥ 30	AHI < 30	p Value
Mandibular internal width, mm	88.5±5.5	90.4±2.8	.240
Mandibular divergence,°	77.8±5.3	77.6±4.6	.910
Mandibular bony thickness, mm	6.5±1.1	7.0±1.3	.410
Mandibular internal length, mm	54.2±4.3	52.6±4.0	.450
Area, cm²	34.7±7.1	30.4±2.4	.023*
Tongue volume, cm³	76.9±12.5	82.2±10.1	.300
Soft palate volume, cm³	6.2±2.4	5.6±2.0	.550
Lateral pharyngeal wall volume, cm³	20.4±4.1	20.4±1.6	.990

All mandibular parameters were based on the mandibular base plane. *p<.05, (Mann-Whitney U-test) AHI, apnea hypopnea index

differences in any morphologic parameters, such as the mandibular internal width (p = .69), mandibular divergence (p =.73), mandibular bony thickness (p = .65), mandibular internal length (p =.58), area (p =.97), tongue volume (p = .69), soft palate volume (p = .57), and lateral pharyngeal wall volume (p =.81) between obese and nonobese patients with OSAHS (Table 2a). We next analyzed the OSAHS group according to those with an AHI greater than 30 (n = 24, severe OSHAS) and those with an AHI less than 30 per hour (n = 7, mild to moderate OSAHS). There was significant difference in area on the mandibular bone plane between the severe and the mild to moderate OSAHS groups, whereas there were no significant differences in any other morphologic parameters (Table 2b).

Correlation analyses among 3D MRI parameters were performed to clarify the direct relationships of these parameters. Mandibular internal length correlated with area (r = 0.46, p = 0.01) and mandibular divergence (r = - 0.58, p = 0.001), thickness (r = - 0.23, p = 0.18), and tongue volume (r = 0.36, p = .049). In contrast, tongue volume did not correlate with BMI or AHI. AHI correlated with lateral pharyngeal wall volume (r = 0.39, p = .035) but not with mandibular internal width, mandibular divergence, mandibular bony thickness, mandibular internal length, area, soft-palate volume, or tongue volume.

For the next series of studies, a logistic regression analysis for OSAHS was performed. Mandibular divergence and area showed a significant odds ratio of 4.87 (95% confidence interval, 0.69-34.4; p = .11) and 2.51 (95% confidence interval, 0.75-8.36; p = .13), respectively, whereas the odds ratio of mandibular internal length was not significant (odds ratio, 0.92; p = .94).

DISCUSSION

There are 3 novel findings in this study that may contribute to the understanding of the pathogenesis of OSAHS in Japanese men. First, the mandible in the patients with OSAHS had a wider mandibular divergence, a smaller mandibular internal length, and a smaller area at the mandibular base plane than that in the control subjects. Second, there were no significant differences in the mandibular bone parameters between the obese and nonobese patients with OSAHS. Third, tongue, soft palate, and lateral pharyngeal wall volumes were not significantly different between the OSAHS and control groups, although lateral pharyngeal wall volume correlated with AHI.

There were several limitations in this study. Patients were awake and respiratory gating was not considered. Trudo et al reported that there is a 19% decrease in airway volume (p = .03) and a 7% increase in the thickness of lateral walls (p = .04) both in the retropalatal region during sleep in nonapneic patients compared with when they are awake.[25] Cine MRI studies have demonstrated that the airway in patients with apnea reaches its maximum size at maximum expiration and narrows to a minimum at the end of expiration, which appears to be heading toward a closed position[14]. However, the influence of being awake and respiration might be minimal for the morphologic analyses of the mandible, tongue, soft palate, and lateral pharyngeal wall.

Another limitation of this study is the difficulty in the 3D volumetric MRI reconstruction of the maxilla. We found it difficult to trim and extract the maxilla because of its complicated structure and the abundance of surrounding tissues. Not only the mandible, but also the maxilla could be important anatomic risk factors for patients with OSAHS.

To the best of our knowledge, there are only 2 studies that have examined the relationship between the cross-sectional area of the mandible and OSAHS. One is a recent report showing that a small mandible is not characteristic in children with OSAHS who do not have apparent craniofacial abnormalities.[26] The other is an earlier report by Shelton et al demonstrating that AHI correlates with the area enclosed by the mandibular ramus at the level of the hard palate and the distance from the teeth to the midpoint of the line between the posterior borders of the ramus of the mandible halfway between the hard palate and the inferior level of the mandible in adults.[27] We performed analyses by 3D volumetric MRI reconstruction and demonstrated that Japanese men with OSAHS had characteristic anatomic features at the bottom part of the mandible. Our previous study using MRI showed that many craniofacial features of patients with OSAHS are particularly associated with each obstructive site and that the features of retrognathia and micrognathia are closely associated with OSAHS, in which the retroglossal level is included as an obstructive site.[28] The present data suggest that the collapse at the retroglossal level due to micrognathia might have a stronger influence on the occurrence of OSAHS than does the collapse at the retropalatal and mesopharyngeal levels in Japanese men with OSAHS.

The collapse along the pharynx is due to 2 anatomic abnormalities, namely, soft tissue and craniofacial abnormalities. Patients with OSAHS are particularly at risk due to the increased volumes of the lateral pharyngeal wall and tongue. Lowe et al determined the sizes of the tongue, soft palate, and pharyngeal airway size by CT and reported that Caucasian patients with OSAHS also have larger tongue, soft-palate, and upper-airway volumes than do control subjects.[7] Recent studies providing important information have focused on the doughnut theory rather than on the simple-hole theory. Investigators at the University of Pennsylvania have provided evidence that lateral pharyngeal wall thickening is singularly associated with upper airway narrowing during sleep and that patients with sleep apnea have abnormally thick lateral pharyngeal walls that encroach on the pharyngeal airway, even after adjustment for covariates, including parapharyngeal fat, sex, and craniofacial configuration in Caucasians.[4, 13-15] However, in the present study, tongue, soft palatal, and lateral pharyngeal wall volumes were not significantly different between the OSAHS and control groups. In addition, tongue, soft palatal, and lateral pharyngeal wall volumes did not positively correlate with BMI. Moreover, no significant differences in 5 mandibular parameters between obese and nonobese patients with OSAHS were found, although 3 of 5 such parameters were significantly different between the OSAHS and control groups. In agreement with results of previous investigations in Asian men with OSAHS,[16, 17] our findings did not demonstrate increased parapharyngeal adiposity in Japanese patients with OSAHS; however, the findings suggest that OSAHS is enhanced by certain craniofacial morphologies.

Craniofacial abnormalities may be apparent anatomic predispositions for Japanese patients with OSAHS; however, we cannot conclude that it is the most important risk factor for OSAHS. Pharyngeal collapse during sleep in patients with OSAHS may be caused not only by structural abnormalities, but also by impairments in neural regulation. By eliminating the neural control mechanism, Isono et al have recently demonstrated that closing pressures of the passive pharynx are distinctively higher in patients with OSAHS than in age- and BMI-matched normal control subjects.[29] In addition, our previous study has demonstrated that, among young nonobese, normocapnic patients with OSAHS with normal craniofacial morphologies but with hypertrophied tonsils, there were significant differences in central chemosensitivity between good responders and poor responders to surgery, suggesting that not only anatomic factors, but also neurologic factors are important in the pathogenesis of OSAHS.[30] Further research is required to determine how upper-airway collapse during sleep is mediated by anatomic and neurologic factors in patients with OSAHS.

In conclusion, patients with OSAHS have specific anatomic morphologies in the bottom part of the mandible. However, increased upper-airway soft-tissue volume was not proven to be an important risk factor for Japanese men with OSAHS. Investigators and clinicians must realize that ethnicity may modify the effects of obesity and abnormal craniofacial anatomy as risk factors for the pathogenesis of OSAHS.

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