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Oropharyngeal Crowding Closely Relates to Aggravation of OSA

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BACKGROUND: Obesity is known to be an important risk factor for OSA; however, OSA can also be seen in nonobese patients with a small maxilla and/or mandible as well as in all obese patients with such features. Thus, we hypothesized that regional factors, oropharyngeal crowding associated with fat deposition, and maxillomandibular enclosure size closely related to the severity of OSA.

METHODS: A total of 703 male Japanese subjects were enrolled; theywere classified into obese (BMI $\geq$ 30 kg/m^2; n = 158) and nonobese (BMI $<$ 30 kg/m^2; n = 545) groups. Using lateral cephalometric analysis, we measured the tongue size (TG), lower face cage (LFC), and TG/LFC ratio (ie, oropharyngeal crowding) to evaluate the state of upper airway crowding. The correlations between these cephalometric measurements and BMI, age, and the apnea-hypopnea index (AHI) were evaluated.

RESULTS: In obese subjects, the TG/LFC ratio, BMI, and TG positively correlated with AHI, whereas, in nonobese subjects, age, BMI, and TG/LFC significantly correlated with AHI. Subsequent stepwise multiple linear regression analysis revealed that the variables associated with AHI differed between obese and nonobese OSA subjects, although BMI and TG/LFC were significantly associated with AHI in both groups. In particular, the contribution of TG/LFC to AHI was larger than that of BMI in the obese group.

CONCLUSIONS: Oropharyngeal crowding is a local anatomic factor that independently relates to the severity of OSA in both obese and nonobese patients; the more crowded the upper airway, the more severe the OSA. CHEST 2016; 150(2):346-352

KEY WORDS: cephalometry; craniofacial morphology; obesity; sleep apnea; upper airway

ABBREVIATIONS: AHI = apnea-hypopnea index; ANB = angle of the maxilla-nasion-mandible; LFC = lower face cage; PSG = polysomnography; SNA = angle of the sella-nasion-maxilla; SNB = angle of the sella-nasion-mandible; TG = tongue size; TG/LFC = ratio between tongue size (TG) and lower face cage

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OSA is a sleep disorder that has substantial adverse affects, especially on the cardiovascular system.[1] Obesity, which is associated with deposition of adipose tissue around both the tongue and upper airway, has been widely accepted as the most recognized general anatomic risk factor for developing OSA.[2] However, previous reports have demonstrated that local risk factors (eg, restricted craniofacial structure) also relate to the development/worsening of OSA in nonobese people.[3-6] It remains to be elucidated, however, why individuals with these general and/or local risk factors do not develop or suffer from severe OSA.

To partially answer this question, we previously demonstrated that obese individuals with excessive soft tissue inside the oral cavity do not necessarily develop OSA if the jaw size is large relative to the amount of soft tissue.[7] Conversely, an obese patient is highly likely to have OSA when the jaw size is not sufficiently large relative to the tongue size (TG), a phenomenon known as oropharyngeal crowding.[7]

It can be speculated that, if this local characteristic is an adequate anatomic reflection of upper airway collapsibility, the OSA would become more severe as the oropharynx becomes more crowded because of an imbalance between the tongue and jaw size. Furthermore, if this is the case, then the dose-dependent anatomic relationship between oropharyngeal crowding and the OSA severity may also be identified in a nonobese subpopulation.

To test these hypotheses, we first investigated whether oropharyngeal crowding is a reasonable local parameter for the prediction of the severity of OSA. Subsequently, we compared the cephalometric variables related to oropharyngeal crowding in obese and nonobese patients with OSA and evaluated the significance of these potential associations for the prediction of the severity of OSA.

Material and Methods

Subjects

The study protocol was approved by the Ethics Committee for Human Research of the Neuropsychiatric Research Institute, Tokyo, Japan (approval no. 98), and was conducted in accordance with the amended Declaration of Helsinki. Informed consent was provided by all eligible subjects.

Eligible patients were consecutive patients who visited outpatient clinics of the Yoyogi Sleep Disorder Center, Tokyo, from January 2010 to December 2012, seeking diagnosis and treatment for suspected OSA, as indicated by subjective daytime sleepiness, loud snoring, or apnea while asleep and witnessed by their family members. The inclusion criteria were as follows: men who were diagnosed with OSA based on clinical interview and diagnostic overnight polysomnography (PSG) and were aged $\geq$ 20 and $<$ 60 years. The subjects were classified into two subgroups according to BMI: obese OSA (BMI $\geq$ 30 kg/m^2) and nonobese OSA (BMI $<$ 30 kg/m^2) groups.[8] The exclusion criteria were as follows: patients who did not meet the above inclusion criteria, women, and patients who had received prior otolaryngological surgery.

Sleep Study and PSG Scoring

PSG recordings included a four-channel EEG (C_3/A_2, C_4/A_1, O_1/A_2, O_2/A_1), electrocardiogram, electrooculogram, submental electromyogram, electromyogram in both legs, airflow measurements with a nasal pressure transducer together with an oronasal thermal sensor, oxygen saturation, thoracoabdominal movements using respiratory inductance plethysmography with a transducer placed around the chest and abdomen, snoring sounds recorded by a microphone, and the body position of the patient. Board-certified sleep technologists manually scored the sleep stages, respiratory events, and EEG arousals every 30 s according to the established criteria.[9,10] An apneic event was defined as a drop in the peak cessation of airflow for 10 s, as measured by the oronasal thermal sensor. A hypopnea event was defined as a decrease in airflow of $\geq$ 30% lasting at least 10 s upon nasal pressure transducer measurements, associated with a decrease of

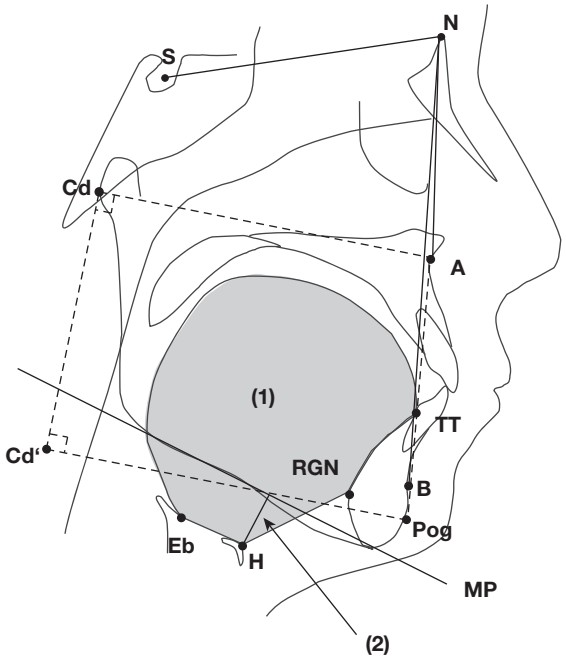

Figure 1 – *Definitions of cephalometric variables. S = sella; A = subspinale; B = supramentale; Cd = medial condylar point of the mandible; Cd′ = the point where Pog projects on the perpendicular line to the Cd-A line at the Cd point; Eb = base of epiglottis; H = hyoid bone; MP = mandibular plane, N = nasion; Pog = pogonion; RGN = retrognathia; TT = tongue tip. (1) Tongue: tongue size is defined as the area outlined by the dorsal configuration of the tongue surface and lines that connect the TT, RGN, H, and Eb. The lower face cage is defined as a trapezoid by Cd-A-Pog-Cd′ (dotted lines). (2) MP-H: perpendicular distance from the anterosuperior point of the hyoid bone to the mandibular plane.*

≥ 4% in oxygen saturation measured by pulse oximetry (Spo_2) from the pre-event baseline, or a decrease in airflow ≥ 50% lasting at least 10 s associated with a decrease in Spo_2 of ≥ 3% from the pre-event baseline or the event associated with an arousal.[10] The apnea-hypopnea index (AHI) was calculated as the average number of apneas and hypopneas per hour of sleep on the diagnostic overnight PSG.

Cephalometric Assessments

The upper airway structure easily varies depending on the changes in head and jaw position[11]; therefore, in the present study, cephalometric assessment was performed in comparable terms as follows:[7,12] briefly, a lateral cephalometric radiograph was obtained for each subject in the upright position with natural head posture using a pair of earpieces. First, the subjects were instructed to have their upper and lower teeth lightly in contact in a natural position and to breathe slowly. The radiograph was taken at the end of expiration, and the exposure parameters were arranged to clearly visualize bony as well as soft-tissue landmarks. Measurements of cephalometric parameters were executed as described in our previous report[7] (Fig 1). Briefly, the lower face cage (LFC; a dotted trapezoid in Fig 1) was determined as the maxillomandibular size (ie, bony enclosure size of the upper airway). TG was defined as the area outlined by dorsal configuration of the tongue surface and lines that connect the tongue tip, retrognathia, hyoid bone, and base of the epiglottis. By using these definitions, anatomical balance was calculated as the ratio between TG and LFC (TG/LFC).[7,12]

Statistical Analyses

All statistical analyses were computed using SPSS (version 23 for Windows; SPSS Japan, Inc.). The normality of data distribution was assessed using the Shapiro-Wilk test. Data are shown as the mean ± SD. Because the AHI was found to be non-normally distributed, the AHI was logarithmically transformed before the subsequent analyses.[13] To identify the variables that affect the AHI, the following serial analyses were performed for both the obese and nonobese subjects, similarly to in previous reports:[3,14] Welch t test was used for comparing parameters between obese and nonobese subjects, and Cohen d (the effect size) was used to investigate differences between the obese and nonobese groups. Typically, Cohen d values of ≤ 0.2, approximately 0.5, and ≥ 0.8 reflect generally small, moderate, and large effect sizes, respectively.[15,16] Next, Pearson product-moment correlation coefficients were analyzed to examine the relationships among age, BMI, cephalometric variables, and log-transformed AHI.[13] Results of the analysis are expressed as the correlation coefficients and P value. Finally, stepwise multiple regression analysis was used to investigate the associations between log-transformed AHI and each variable that showed significant associations in the Pearson product-moment correlation coefficient analysis.[13] These analyses were performed to ensure the assumptions of no presence of multicollinearity, linearity, homoscedasticity, and autocorrelation. For all analyses, a P value $< .05$ was considered to indicate statistical significance.

Results

During the study period, a total of 1,099 male subjects were newly diagnosed with OSA. Among them, 706 subjects were aged ≥ 20 and < 60 years. Of these, three subjects were excluded because of the presence of prior otolaryngological surgery. Obese subjects, as defined by a BMI of ≥ 30 kg/m^2, accounted for 158 of the 703 subjects (22.5%). Accordingly, nonobese subjects (BMI < 30 kg/m^2) accounted for the remaining 545 subjects (77.5%). The anthropometric and cephalometric data of both groups are presented in Table 1. Significant differences were found between obese and nonobese subjects in the AHI (obese, 47.1 ± 30.7 events/h; nonobese, 20.6 ± 19.8 events/h; $P < .001$, Cohen d = 1.17), TG (obese, 39.9 ± 3.8 cm^2; nonobese, 36.5 ± 3.7 cm^2; $P < .001$, Cohen d = 0.91), TG/LFC (obese, 0.588 ± 0.057; nonobese, 0.557 ± 0.057; $P < .001$, Cohen d = 0.54), LFC (obese, 68.4 ± 7.1 cm^2; nonobese, 65.8 ± 6.2 cm^2; $P < .001$, Cohen d = 0.41), angle of the sella-nasion-maxilla (obese, 83.2 ± 3.6°; nonobese,

TABLE 1] Descriptive Variables of the Subjects

Parameter	Total (N = 703)	Obese (n = 158)	Nonobese (n = 545)	t Value (df)	d
Age, y	43.1 ± 9.2	41.9 ± 9.5	43.4 ± 9.2	−1.795 (247.94)	0.16
BMI, kg/m^2	26.6 ± 4.8	33.6 ± 3.5	24.6 ± 2.9[a]	29.126 (225.08)	2.96
AHI, events/h	26.5 ± 25.3	47.1 ± 30.7	20.6 ± 19.8[a]	10.214 (196.19)	1.17
SNA, °	82.3 ± 3.8	83.2 ± 3.6	82.1 ± 3.8[b]	3.360 (267.24)	0.29
SNB, °	77.6 ± 4.0	78.5 ± 3.5	77.4 ± 4.1[b]	3.181 (288.39)	0.28
ANB, °	4.7 ± 2.5	4.7 ± 2.5	4.7 ± 2.5	0.354 (259.35)	0.00
MP-H, mm	20.3 ± 6.0	22.1 ± 5.7	19.8 ± 6.0[a]	4.329 (269.5)	0.44
TG, cm^2	37.3 ± 4.0	39.9 ± 3.8	36.5 ± 3.7[a]	10.140 (253.55)	0.91
LFC, cm^2	66.3 ± 6.5	68.4 ± 7.1	65.8 ± 6.2[a]	4.198 (231.38)	0.41
TG/LFC	0.564 ± 0.059	0.588 ± 0.057	0.557 ± 0.057[a]	5.918 (254.91)	0.54

Values are expressed as the mean ± standard deviation; Welch t test was used for analyzing difference between obese (BMI ≥ 30 kg/m^2) and nonobese (BMI < 30 kg/m^2) patients. AHI = apnea-hypopnea index; ANB = angle of the maxilla-nasion-mandible; d = Cohen d; df = degrees of freedom; LFC = lower face cage; MP-H = perpendicular distance from the anterosuperior point of the hyoid bone to the mandibular plane; SNA = angle of the sella-nasion-maxilla; SNB = angle of the sella-nasion-mandible; TG = tongue size; TG/LFC = the ratio between tongue size and lower face cage.
[a]$P < .001$ vs obese.
[b]$P < .01$ vs obese.

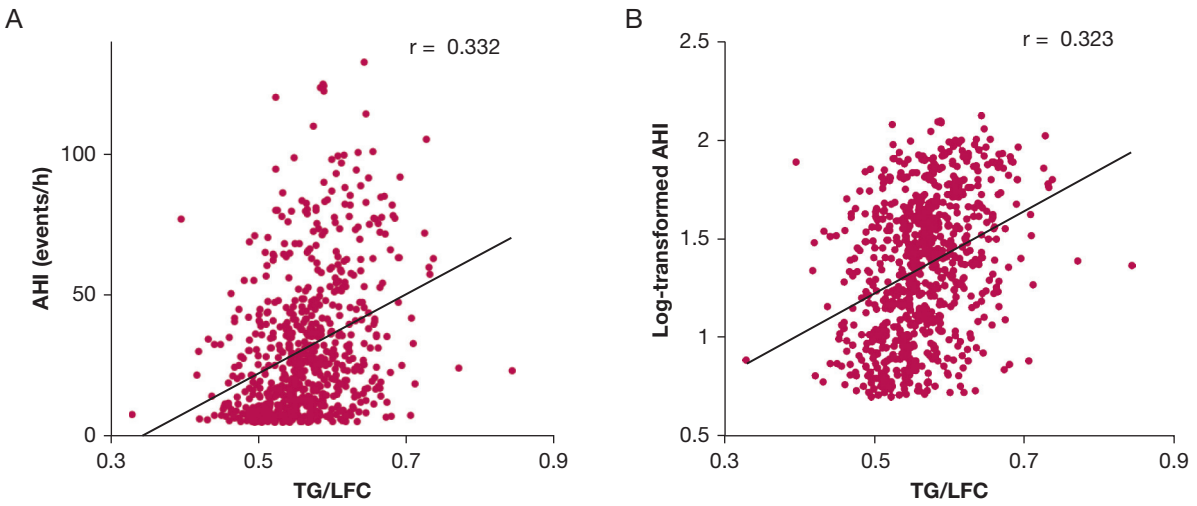

Figure 2 – *Relationship between (A) AHI or (B) log-transformed AHI and TG/LFC in 703 OSA subjects. (A) Correlation coefficient = 0.332, P < .001, and (B) correlation coefficient = 0.323, P < .001 by using Pearson product-moment correlation coefficients. AHI = apnea-hypopnea index; TG/LFC = ratio between the tongue size and lower face cage (ie, degrees of oropharyngeal crowding).*

82.1 ± 3.8°; $P = .001$, Cohen d = 0.29), and angle of the sella-nasion-mandible (obese, 78.5 ± 3.5°; nonobese, 77.4 ± 4.1°; $P = .002$, Cohen d = 0.28). In particular, the effects sizes for AHI and TG were large, indicating that these might have significant statistical power.

For the entire cohort (N = 703), there was a significant correlation between TG/LFC and AHI (r = 0.332, $P < .001$) (Fig 2A). A significant correlation was also found between TG/LFC and log-transformed AHI (r = 0.323, $P < .001$) (Fig 2B). In obese subjects, Pearson product-moment correlation coefficients revealed that log-transformed AHI significantly correlated with the TG/LFC (r = 0.472; $P < .001$), TG (r = 0.326; $P < .001$), perpendicular distance from the anterosuperior point of the hyoid bone to the mandibular plane (MP-H; r = 0.255; $P = .001$), BMI (r = 0.254; $P = .001$), and angle of the maxilla-nasion-mandible (r = 0.168; $P = .034$), but not with age, sella-nasion-maxilla, sella-nasion-mandible, or LFC (Table 2). Among these parameters, TG/LFC showed the highest positive correlation. Meanwhile, in nonobese subjects, log-transformed AHI significantly correlated with age (r = 0.341; $P < .001$), BMI (r = 0.278; $P < .001$), TG/LFC (r = 0.233; $P < .001$), TG (r = 0.215; $P < .001$), and MP-H (r = 0.092; $P = .032$).

Subsequently, a stepwise multiple linear regression analysis was conducted with the independent variables that showed significant correlations with log-transformed AHI according to Pearson product-moment correlation coefficients (Table 3). In obese subjects, TG/LFC and BMI were found to be significantly associated with log-transformed AHI, explaining 29.4% of its variance

TABLE 2] Correlational Coefficients of the Respective Measurement Parameters to Log-Transformed AHI

	Obese		Nonobese	
Parameter	CC	*P* Value	CC	*P* Value
Age	0.102	NS	0.341	< .001
BMI	0.254	.001	0.278	< .001
SNA	−0.036	NS	0.011	NS
SNB	−0.154	NS	−0.033	NS
ANB	0.168	.034	0.069	NS
MP-H	0.255	.001	0.092	.032
TG	0.326	< .001	0.215	< .001
LFC	−0.151	NS	−0.017	NS
TG/LFC	0.472	< .001	0.233	< .001

Values are expressed as the correlation coefficient by using Pearson product-moment correlation coefficients. Obese (BMI ≥ 30 kg/m^2); nonobese (BMI < 30 kg/m^2). CC = correlation coefficient; NS = not significant. See Table 1 legend for expansion of other abbreviations.

TABLE 3] Stepwise Multiple Linear Regression Analysis With Log-Transformed AHI as the Dependent Variable

Obese (BMI ≥ 30 kg/m^2, n = 158)					
R^2 (AdR^2)	Predictor	B (95.0% CI)	β (95.0% CI)	t Value	*P* Value
0.294 (0.285)	(Constant)	−1.249 (−1.960 to −0.539)		−3.474	.001
	TG/LFC	3.130 (2.261-4.000)	0.480 (0.347-0.613)	7.112	< .001
	BMI	0.028 (0.014-0.043)	0.268 (0.134-0.412)	3.972	< .001
Nonobese (BMI < 30 kg/m^2, n = 545)					
R^2 (AdR^2)	Predictor	B (95.0% CI)	β (95.0% CI)	t Value	*P* Value
0.205 (0.200)	(Constant)	−1.723 (−2.252 to −1.195)		−6.407	< .001
	Age	0.019 (0.014-0.0.024)	0.307 (0.226-0.388)	7.927	< .001
	BMI	0.044 (0.029-0.059)	0.226 (0.149-0.345)	5.628	< .001
	TG/LFC	1.220 (0.429-2.011)	0.123 (0.043-0.203)	3.030	.003
	MP-H	0.009 (0.002-0.016)	0.098 (0.022-0.174)	2.541	.011

AdR^2 = adjusted R squared; B = unstandardized coefficients; β = standardized coefficients. See Table 1 legend for expansion of other abbreviations.

($r^2 = 0.294$, $P < .001$). On the basis of standardized coefficients (β), TG/LFC (0.480) appeared as the most highly contributing factor of log-transformed AHI, with the β value of TG/LFC being larger than that of BMI (0.268).

On the other hand, in nonobese subjects, age, BMI, TG/LFC, and MP-H were significantly associated with log-transformed AHI, explaining 20.5% of its variance ($r^2 = 0.205$, $P < .001$). The β value of age (0.307) was larger than those of BMI (0.226), TG/LFC (0.123), and MP-H (0.098).

Discussion

To our knowledge, this is the first report that successfully demonstrated that oropharyngeal crowding, as defined by anatomical imbalance of the upper airway, independently relates closely to the severity of OSA in both obese and nonobese patients. That is, the more crowded the upper airway, the more severe the OSA.

Figure 3 provides a schematic illustration to explain the results of the present study. As seen in this figure, obesity increases the degree of oropharyngeal crowding, resulting in increased OSA severity (Fig 3, bottom row), as widely recognized.[17] However, OSA is also observed in nonobese individuals who might not have a thick neck, but who rather have a small maxilla and/or mandible.[17] In such cases, even if the amount of soft tissue is normal, the cross-sectional area of the upper airway may become narrow and the hyoid bone could be more caudally positioned, as seen in both obese and nonobese patients (Fig 3, top and bottom). A larger MP-H in nonobese OSA, indicating a more caudally positioned hyoid bone, can be interpreted as a consequence of excessive soft tissue resulting from oropharyngeal crowding (Fig 3, top). If so, longitudinal tension along the pharyngeal airway, which significantly affects the severity of OSA, can, to some extent, be estimated by focusing on the hyoid bone position in patients with OSA. In turn, the contribution of MP-H in the prediction of AHI was low in obese people according to the stepwise multiple linear regression analysis (Table 3). Although the mechanism of the difference between the two subgroups needs to be further investigated, lung volume reduction resulting from obesity acts to decrease the longitudinal upper airway tension in obese patients with OSA. This obesity-related effect may partially offset the caudal repositioning of the hyoid bone; thereby, the MP-H as a predictor of AHI might be weakened in obese subjects.

Isono and colleagues demonstrated that the cross-sectional area of the upper airway decreases as the severity of OSA becomes higher at a given intraluminal airway pressure.[18] Tsuiki and co-investigators further suggested that the cross-sectional area of the upper airway decreases more in individuals with vs without oropharyngeal crowding.[7] On the basis of these reports, we believe it is reasonable to suggest that the severity of OSA is dose-dependent on the amount of oropharyngeal crowding, as shown in Figure 2. This speculation is partly supported by the fact that a step-increment of the protrusive range of the mandible in oral appliance therapy dose-dependently improves the AHI, as well as Spo_2, by normalizing the oropharyngeal crowding.[19-21]

In this study, we succeeded in detecting the effects of oropharyngeal crowding on the development of OSA in

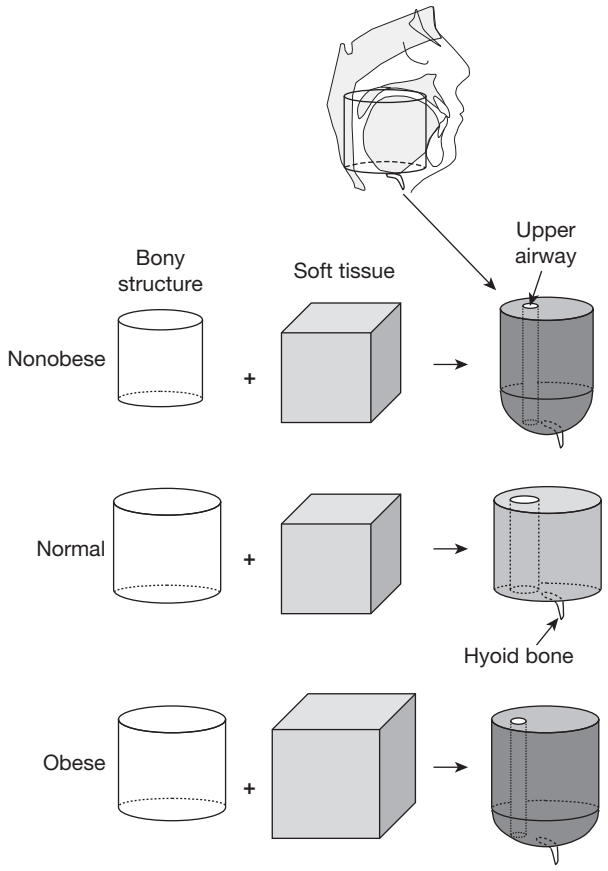

Figure 3 – *Schematic explanations of the interaction between the upper airway bony enclosure and soft tissue contributing to the pharyngeal airway size. Excessive soft tissue in relation to obesity (ie, lower part) or a small maxilla/mandible (ie, upper part) results in pharyngeal airway narrowing and caudal displacement of the hyoid bone. The presence of the two different factors is associated with an easily collapsing upper airway and with the severity of obstructive sleep apnea. According to this mechanical simplification of the anatomical structures surrounding the pharyngeal airway, the balance between the craniofacial bony enclosure size and the amount of soft tissue is considered to determine the airway size. Part of this illustration is referred to in previous reports.*[11,17]

not only obese but also nonobese patients (Table 3), in addition to known risk factors such as obesity and aging. There is no doubt that an increased volume of adipose tissue in the surrounding neck, which is related to obesity, directly influences narrowing of the airway lumen and upper airways. Moreover, increased tongue weight has been demonstrated to positively correlate with obesity and decreased lung volume, and to consequently result in reduction of caudal traction and increased pharyngeal airway collapsibility.[22-24] Similarly, age is another important factor contributing to OSA, as a result of the accompanying increase in the related pharyngeal airway collapsibility.[25] However, considering that a previous large epidemiologic study reported that approximately 56% of patients with OSA (AHI $\geq$ 15 events/h) were nonobese, and that the prevalence of OSA in patients older than 60 years of age is leveling off or slightly increasing,[26] these results suggest the necessity of patient-tailored treatment that cannot be solely determined on the basis of the severity of the OSA (ie, the AHI).

The results of the present study are in line with previous findings that craniofacial skeletal anatomic abnormalities are important risk factors of OSA (Table 2).[3,4,12,27] The major characteristics of such studies included the effects of greater mandibular retroposition and inferior displacement of the hyoid bone.[28] In this study, we reconfirmed the findings by Yu et al[28] and demonstrated that the relative position between the maxilla and mandible (ie, angle of the maxilla-nasion-mandible) is important in the development of OSA in both obese and nonobese subjects.

This study has several limitations. First, all subjects were recruited from only one sleep disorder center, which might cause some sampling bias. Second, although we succeeded in enrolling a relative large number of subjects in each group, they were all men. Because there are known sex differences in the regional distribution of fat deposition,[29] future research evaluating the relationship between the AHI and cephalometric variables in female subjects is needed. Third, our structural image analyses were conducted by using lateral cephalometric radiographs. MRI[30] and CT[31] can measure both the bony structure size and amount of the soft tissue, and allow for reconstruction of three-dimensional images of the whole upper airway structure. However, our two-dimensional cephalometric analysis has the advantage of easy applicability in general clinical settings, which enabled us to analyze 703 OSA subjects within a relatively short timeframe. Future studies evaluating anatomical imbalance using volumetric analyses of the constituents of the upper airway by three-dimensional MRI or CT scans are warranted, and, if the findings can be compared with concurrent two-dimensional cephalometry, will increase the importance of such two-dimensional analysis. Finally, in this study, BMI was used as the only index of obesity used to evaluate a variety of obese habitus, because other parameters, such as the neck/abdominal circumferences and waist-hip ratio, were not routinely recorded in our clinic. Future studies analyzing the different types of obesity using such anthropometric parameters related to oropharyngeal crowding are needed. Nevertheless, despite these limitations, we still believe that the concept of a close relationship between regional obesity and worsening of OSA is widely applicable in clinical settings.

In conclusion, our study suggests that oropharyngeal crowding is a local anatomic parameter that independently predicts the severity of OSA in both obese and nonobese patients. The more crowded the upper airway, the more severe the OSA.

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Author contributions: E. I. had full access to the data in this study and takes responsibility for the integrity of the data and accuracy of the data analysis and contributed to the conception, study design, data collection, interpretation of data, and manuscript drafting. S. T. contributed to the conception, study design, interpretation of data, and writing of the manuscript. K. M. undertook data collection and analysis. I. O. assisted with the statistical evaluation and data analysis. Y. I. contributed to the conception, interpretation of data, and manuscript drafting.

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