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Original Research

SLEEP DISORDERS

Oropharyngeal Crowding and Obesity as Predictors of Oral Appliance Treatment Response to Moderate Obstructive Sleep Apnea

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Background: **Oral appliances are increasingly prescribed for patients with moderate obstructive sleep apnea (OSA) instead of nasal CPAP. However, the efficacy of oral appliances varies greatly. We hypothesized that oral appliances were not efficacious in patients with moderate OSA who were obese with oropharyngeal crowding.**

Methods: **Japanese patients with moderate OSA were prospectively and consecutively recruited. The Mallampati score (MS) was used as an estimate of oropharyngeal crowding. Follow-up polysomnography was performed with the adjusted oral appliance in place. Responders were defined as subjects who showed a follow-up apnea-hypopnea index (AHI) of <5 with $>50\%$ reduction in baseline AHI.**

Results: **The mean baseline AHI was reduced with an oral appliance from 21 ± 4 to 9.8 ± 8 in 95 subjects. Thirty-five patients were regarded as responders. Logistic regression analyses revealed that both MS and BMI could individually predict the treatment outcome. When the cutoff value of BMI was determined to be 24 kg/m^2 based on a receiver operating characteristic curve, 53 obese patients (ie, BMI >24 kg/m^2) with an MS of class 4 were indicative of treatment failure with a high negative predictive value (92) and a low negative likelihood ratio (0.28).**

Conclusions: **We conclude that patients with moderate OSA who are obese with oropharyngeal crowding are unlikely to respond to oral appliance treatment. This simple prediction can be applied without the need for any cumbersome tools immediately after the diagnosis of OSA.**

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Abbreviations: AHI = apnea-hypopnea index; LR− = negative likelihood ratio; LR+ = positive likelihood ratio; MS = Mallampati score; nCPAP = nasal CPAP; OSA = obstructive sleep apnea; PSG = polysomnography

Reports have documented that oral appliances providing mandibular advancement are now indicated not only for individuals with mild obstructive sleep apnea (OSA) but also for those with moderate OSA.[1,2] However, in the treatment of patients with moderate OSA, sleep dentists and physicians often must decide whether to use either nasal CPAP (nCPAP) or an oral appliance immediately after the diagnosis based on a consideration of not just efficacy but also compliance, long-term side effects, and the patient's preference. The identification of simple and reliable predictors of treatment outcome with oral appliance therapy is especially elusive, because oral appliances are less efficacious than nCPAP in cases of moderate OSA.[1,2]

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Clinically, obesity is a factor that increases the vulnerability to upper airway collapse due to redundant oropharyngeal soft tissue.[3,4] It has also been reported that mandibular advancement did not successfully improve velopharyngeal airway patency in obese people.[5] In addition, the tendency for upper airway collapse is increased when patients with OSA have an anatomic imbalance of the upper airway in which the amount of soft tissue inside the craniofacial bony enclosure (eg, tongue) is excessive relative to the size of the craniofacial bony enclosure (eg, maxilla, mandible).[6,7] These reports suggest that the outcome of oral appliance treatment could be predicted by focusing on obesity and an anatomic imbalance of the upper airway. Therefore, we hypothesized that obese patients with OSA with an oral cavity that is more crowded with soft tissue would not respond well to oral appliance therapy because of a high likelihood of an increased collapsibility of the upper airway.

The Mallampati score (MS) enables us to instantaneously evaluate the state of crowding in the oropharyngeal region caused by a large tongue and/or a small craniofacial bony enclosure.[8,9] In the present study, we prospectively investigated associations among MS, obesity, and the response to treatment with an oral appliance in Japanese patients with moderate OSA.

Materials and Methods

Patients

This study was conducted in accordance with the amended Declaration of Helsinki, and the study protocol was approved by the ethics committee for human research at the Neuropsychiatric Research Institute in Tokyo, Japan (approval number #14, #48). Detailed study objectives and potential risks were explained to each patient, and written informed consent was obtained before initiation of the study. All patients were diagnosed with OSA (apnea-hypopnea index [AHI] >5) based on clinical interviews and a diagnostic overnight polysomnography (PSG) following standard parameters.[10,11] Patients with mild OSA ($5<\text{AHI}\leq 15$) and severe OSA (AHI >30) were not recruited. The inclusion criteria were as follows: male patients with moderate OSA ($15<\text{AHI}\leq 30$) in the initial PSG and age between 25 and 65 years. Patients who met one of the following exclusion criteria were excluded: women, severe periodontitis, insufficient number of teeth, denture user, temporomandibular joint dysfunction, prior otolaryngeal surgery, cardiovascular disease, medically complicated, or medically unstable.

The prospective and consecutive recruitment of patients began in June 2005 and was completed by February 2012. When the inclusion/exclusion criteria were satisfied, an oral appliance was used in 293 patients with moderate OSA who visited our sleep apnea dental clinic. Of these, a total of 95 patients with moderate OSA completed the protocol, including the follow-up PSG, by June 2012 and were considered to be eligible for subsequent analyses.

Mallampati Score

The assessment of MS was performed by the same investigator (S. T.), who was blinded to the PSG data, including the AHI.[8,9] The patient's head was supported by the dental chair to avoid neck extension in the sitting position. The head position was fixed parallel to the Frankfort horizontal plane. The score was assessed by asking the patient to open the mouth maximally without emitting sounds, while protruding the tongue as far as possible. A standard 1 to 4 grading system was used to assign scores: class 1: soft palate and entire uvula visible; class 2: soft palate and portion of the uvula visible; class 3: soft palate visible (may include the base of the uvula); class 4: soft palate not visible. The MS was assessed repeatedly on different days, and the interobserver agreement of MS assessment has been documented in detail by Rosenstock et al.[12]

Additionally, the MS was checked by a simple, quick mouth-opening without support for the head position: patients were instructed not to extend the neck when opening the mouth. The MS obtained with the head position fixed was compared with the MS evaluated with a simple quick mouth-opening.

Oral Appliance

A custom-made monobloc mandibular advancement oral appliance (ASO International, Inc) was inserted for each patient. Detailed information, including fabrication and adjustments, was as described previously.[13]

Study Protocol and Treatment Outcome

The MS was assessed simultaneously with a clinical dental evaluation. When no significant problems occurred after insertion of the oral appliance and an adaptation period (approximately 4 weeks), the lower part of the appliance was ventrally advanced according to the process described elsewhere.[13] A second PSG was then performed with the adjusted oral appliance in place after we confirmed that the patient felt that the final mandibular position was comfortable. Responders were defined as patients who showed a reduction in AHI to <5 in addition to a $>50\%$ reduction compared with the baseline AHI.[13,14]

Statistical Analyses

All statistical analyses were performed using SPSS (version 11.5; IBM) and/or Microsoft Excel-based software unless otherwise stated. Data are presented as mean $\pm$ SD, and paired t tests were used to compare the differences between the baseline and follow-up PSG values for each variable. Unpaired t tests were used to compare the PSG variables between responders and nonresponders. A univariate logistic regression followed by a multivariate logistic regression analysis was performed to investigate contributions to the likelihood of treatment success by incorporating age, MS, BMI, and baseline AHI. The relationship between BMI and MS was investigated using Spearman rank correlation. The patients were divided into nonobese and obese subgroups on the basis of a BMI cutoff point that was obtained from a receiver operating characteristic curve for the prediction of treatment success.[13] Patients were also divided into lower (class 1-3: some airway visible) and higher (class 4: no airway visible) MS subgroups. We prepared 2×2 cross tables for the χ^2 test with the Yates correction where appropriate and a similar table with two layers (ie, MS and BMI) to evaluate the effects of the single or combined use of the two parameters on the responder-nonresponder distribution. A P value <0.05 was considered to indicate statistical significance.

Results

The repeated assessment of MS on different days (day 1 vs day 2) showed good reproducibility, with an intraclass correlation coefficient (95% CI) of 0.81

(0.67-0.89). Comparisons of MS obtained with a fixed head position (day 1 and day 2) and MS evaluated with a simple quick mouth-opening (day 3) also revealed good agreement between the two methods (day 1 vs day 3, 0.74 [0.56-0.85]; day 2 vs day 3, 0.74 [0.56-0.85]).

For the entire study cohort (N = 95), the baseline age and BMI of the patients were 45 ± 10 years and 25 ± 4 kg/m², respectively (Table 1). The baseline AHI at the initial diagnostic PSG was 21 ± 4. The MS was 3.0 ± 1.0. The follow-up AHI with the oral appliance in place was significantly lower than that at baseline (9 ± 8, $P < .001$). There were no significant changes in BMI throughout the study. The 95 patients with OSA were divided into responders and nonresponders according to the responder criterion. There were significant differences in BMI ($P = .02$) and MS ($P = .04$) between responders and nonresponders. No significant difference was observed in the baseline AHI between responders and nonresponders ($P = .69$). The AHI was significantly reduced with the oral appliance in place in both responders ($P < .001$) and nonresponders ($P < .001$).

A univariate logistic regression analysis revealed that both BMI (OR [95% CI], 0.82 [0.71-0.96]; $P = .01$) and MS (0.55 [0.34-0.89], $P = .02$) independently influenced the success of treatment of moderate OSA with an oral appliance. A similar observation was also found for both BMI (0.83 [0.72-0.97], $P = .02$) and MS (0.61 [0.38-0.97], $P = .04$) with a multiple logistic regression analysis (Table 2).

There was no significant correlation between MS and BMI ($P = .95$), which indicated that a higher MS was not necessarily associated with obesity (Fig 1A). Nonresponders tended to have a higher MS (ie, class 4) than responders (Fig 1B).

The patients were divided into lower (ie, class 1 to 3) and higher (ie, class 4) MS subgroups. Nonobese and obese subgroups were also defined with the best BMI cutoff at 24 kg/m² based on the receiver operating characteristic curve (area under the curve = 0.66 ± 0.06 [SE], $P = .01$) (Tables 3, 4). The sensitivity/specificity and positive likelihood ratio/negative likelihood ratio (LR+/LR−) for MS alone were 80/57 and 1.85/0.35, respectively (Table 5). The sensitivity/specificity and LR+/LR− for BMI alone were 63/67 and 1.89/0.56, respectively. A higher negative predictive value was observed for MS (83) than for BMI (75). Notably, the negative predictive value increased to 92 with a lower LR− (0.28) when MS was used in obese patients with OSA.

Table 1—*Clinical Characteristics of Patients According to the Treatment Outcome*

Diagnostic Characteristics	Responders	Nonresponders	Total
Subjects (%)	35 (37)	60 (63)	95
Age, y	45 ± 9	44 ± 10	45 ± 10
BMI, kg/m²	23 ± 3[a]	26 ± 4	25 ± 4
MS	2.7 ± 0.9[a]	3.2 ± 1.0	3.0 ± 1.0
ESS	13 ± 5[a]	11 ± 5	12 ± 5
AHI baseline/h	21 ± 5	20 ± 4	21 ± 4
AHI follow-up/h	2 ± 2[b,c]	13 ± 8[c]	9 ± 8[c]

Values are expressed as the mean ± SD. Responders were defined as patients who showed a follow-up AHI < 5 with a > 50% reduction compared with the baseline AHI. AHI = apnea-hypopnea index; ESS = Epworth Sleepiness Scale; MS = Mallampati score.
[a]$P < .05$ vs nonresponder.
[b]$P < .01$ vs nonresponder.
[c]$P < .01$ vs baseline.

Table 2—*Logistic Regression Analysis of Factors Associated With the Outcome of Treatment With an Oral Appliance in 95 Patients With Moderate OSA*

Diagnostic Characteristics	OR	95% CI	*P* Value
Univariate model			
Age	0.99	0.95-1.04	.70
BMI	0.82	0.71-0.96	.01[a]
MS	0.55	0.34-0.89	.02[a]
AHI baseline	1.10	0.98-1.22	.10
Multivariate model			
BMI	0.83	0.72-0.97	.02[a]
MS	0.61	0.38-0.97	.04[a]

Data are presented as OR and 95% CI. Increases in both BMI and MS are significantly more likely to be associated with treatment failure with an oral appliance in patients with moderate OSA. OSA = obstructive sleep apnea. See Table 1 legend for expansion of other abbreviations.
[a]$P < .05$.

Discussion

The use of oral appliances has been recommended in patients with moderate OSA, although there is a scarcity of evidence-based data to actively promote or discourage the use of such appliances instead of

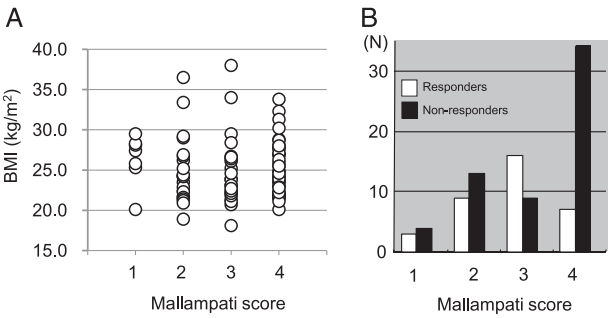

Figure 1. A, The relationship between the Mallampati score and BMI in 95 patients with moderate obstructive sleep apnea (OSA). B, Relationship between the Mallampati score and the response to treatment in 95 patients with moderate OSA. Open bars denote responders, and solid bars are nonresponders. The lack of a significant correlation between the Mallampati score and BMI (A) indicates that oropharyngeal crowding (ie, Mallampati score of class 4) does not necessarily suggest obesity.

Table 3—*Use of Cutoffs for the MS and Obesity Alone for Predicting the Outcome of Treatment With an Oral Appliance*

Variables	Responders	Nonresponders	Total
MS			
Some airway visible	28	26	54
No airway visible	7	34	41
Total	35	60[a]	95
Obesity			
Nonobese	22	20	42
Obese	13	40	53
Total	35	60[b]	95

No airway visible = Mallampati score of class 4; nonobese = BMI ≤ 24; obese = BMI > 24; some airway visible = Mallampati score of class 1-3. See Table 1 legend for expansion of other abbreviation. Note that the obesity cutoff in this study was determined by a receiver operating characteristic curve.

[a]Yates $\chi^2 = 10.7$, $P < .01$ vs responders.

[b]$\chi^2 = 7.81$, $P < .01$ vs responders.

nCPAP.[15] We found that obese patients with moderate OSA and those with an oral cavity that was more crowded with soft tissue did not respond well to treatment with an oral appliance. In addition, there was no significant correlation between MS and BMI, and these two parameters independently predicted the treatment outcome. Therefore, it would be reasonable to assume that the combination of these two independent predictors could provide a better prediction than either parameter alone: nine of 10 obese patients with moderate OSA with MS of class 4 should show treatment failure with an oral appliance (Table 5).

A satisfactory prediction using local (ie, anatomic imbalance) and general (ie, obesity) characteristics would reflect certain anatomic and rheologic mechanisms. First, a previous study demonstrated that weight loss decreased the collapsibility of the upper airway as determined by the critical closing pressure of the pharynx.[16] This could be interpreted to indicate that upper airway collapsibility was greater in obese people than in nonobese people.[3] Kuna and Remmers[3] later speculated that mandibular advancement with an oral appliance could improve the collapsibility of the upper airway by changing the stiffness of the upper airway wall. Although advancement of the mandible using an oral appliance serves to return the increased upper airway collapsibility to normal by temporarily enlarging the size of the bony enclosure, thereby reducing the relative amount of soft tissue inside the bony enclosure (Fig 2),[4,5,17,18] a greater amount of mandibular advancement is required to restore upper airway patency in patients with more increased upper airway collapsibility (Fig 2). However, since the range of mandibular advancement is anatomically limited, there is less chance that patients with increased collapsibility will obtain results as favorable as those in patients without an increased collapsibility. Second, obesity leads to a decrease in lung volume that consequently changes the longitudinal length of the upper airway and reduces the stiffness of the upper airway in patients with OSA.[19] The application of positive airway pressure using nCPAP improves the lung volume by increasing the transmural pressure of the lung and, thus, would normalize the longitudinal dimension of the upper airway. However, this effect on lung volume cannot be expected with mandibular protrusion.

Table 4—*Use of Cutoffs for the MS and Obesity in Combination for Predicting the Outcome of Treatment With an Oral Appliance*

Obesity	MS	Responders	Nonresponders	Total
Nonobese	Some airway visible	17	8	25
	No airway visible	5	12	17
	Total	22	20[a]	42
Obese	Some airway visible	11	18	29
	No airway visible	2	22	24
	Total	13	40[b]	53

Note that the obesity cutoff in this study was determined by a receiver operating characteristic curve. See Table 1 and 3 legends for expansion of abbreviations.

[a]Yates $\chi^2 = 4.59$, $P < .05$ vs responders.

[b]Yates $\chi^2 = 4.72$, $P < .05$ vs responders.

A reliable predictor is needed more for moderate OSA than for mild OSA for two reasons. Patients with mild OSA are basically prescribed oral appliances, and thus the results of the prediction would not affect the selection of treatment.[1,2] Also, prediction of the treatment outcome per se might not be necessary for patients with mild OSA, since the success rate with an oral appliance has already been reported to be good in such patients without the use of any predictive approaches. In contrast to a few reports suggesting that the severity of OSA at baseline predicted the treatment success with an oral appliance,[1,2] our logistic regression analyses did not indicate that baseline AHI significantly contributed to predicting the treatment outcome (Table 1). This difference may be related to the fact that we only considered patients with moderate OSA.

Although our primary objective was to examine the use of MS and obesity for predicting the outcome of treatment with an oral appliance, this study has significant limitations. First, MS may be more or less difficult to measure, since the score might be affected by breathing and tongue position: Subjects often push their tongue down, thus artificially decreasing MS. Therefore, patients were instructed not to breathe through the mouth and not to push the tongue down artificially, which led to acceptable reproducibility for our MS measurement. Second, the predictive ability should be examined further in patients from white populations and from other races because of the race-specific characteristics of a lower BMI in our Japanese samples.[20,21] Thus, the appropriate cutoff values for each race need to be considered on the basis of receiver

Table 5—*Prediction of the Treatment Outcome With an Oral Appliance by the MS, BMI, or Both in Patients With Moderate OSA*

Prediction Variable	MS	Obesity	MS and Nonobese (n = 42)	MS and Obese (n = 53)
Sensitivity	80	63	77	85
Specificity	57	67	60	55
PPV	52	52	68	38
NPV	83	75	71	92
LR+	1.85	1.89	1.93	1.88
LR−	0.35	0.56	0.38	0.28

LR− = negative likelihood ratio; LR+ = positive likelihood ratio; NPV = negative predictive value; PPV = positive predictive value. See Table 1-3 legends for expansion of other abbreviations.

operating characteristic curves. Moreover, such a racial difference may also lead to craniofacial differences, and further studies are needed on the relationship between MS and three-dimensional craniofacial structures, including hard as well as soft tissues around the upper airway.[22] Our results regarding the OR (Table 2) and the negative predictive value (Tables 5) suggested that oral appliances are less indicated for patients with moderate OSA with oropharyngeal crowding than for those with obesity. The results may also vary because of sex, age, and the use of titratable oral appliances.

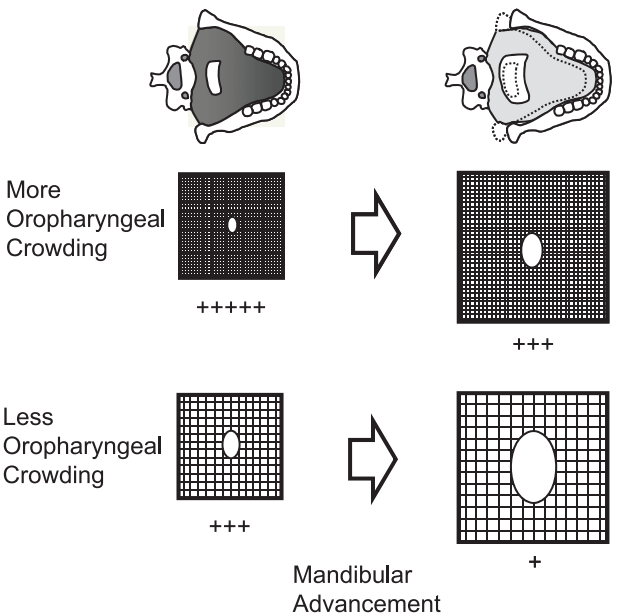

FIGURE 2. Schematic illustration of the possible effects of mandibular advancement by an oral appliance on oropharyngeal crowding in patients with obstructive sleep apnea. An increased shading density indicates increased soft tissue pressure inside the craniofacial bony enclosure. Mandibular advancement by an oral appliance restores the increased upper airway collapsibility to normal by temporarily enlarging the size of the bony enclosure (left to right). A greater number of plus symbols indicates a greater collapsibility of the upper airway. However, a given degree of mandibular advancement is less likely to reduce the collapsibility in patients with more oropharyngeal crowding (upper) compared with those with less oropharyngeal crowding (lower). The increased shading density in patients with more oropharyngeal crowding (upper) does not change as much as that in patients with less oropharyngeal crowding (lower) in response to mandibular advancement.

Although the results are of sufficient power to support the usefulness of the prediction, a large-scale validation study is needed.

The strength of the present prediction model is that it is simple, noninvasive, and inexpensive and does not have time constraints. Thus, it could be widely useful in sleep centers and community practices for deciding upon treatment options without delay after diagnosis. In addition, we demonstrated that a quick mouth-open assessment of MS could be more practical at nondental clinics, as long as the head position was not changed during the assessment of MS. This approach could expedite the application of a practical algorithm in patients with moderate OSA who require either an oral appliance or nCPAP. In obese people with a low MS, predominantly abdominal obesity may explain more of the poor response to oral appliance therapy, since the impact of lung volume on the upper airway may be greater than expected, as mentioned before. Therefore, it might be reasonable to also look at neck and waist circumferences as indicators of the obesity distribution. The combination of our method and the results of other techniques may realize better predictions of the treatment outcome even for patients with severe OSA.[23,24] In conclusion, obese Japanese patients with moderate OSA who have oropharyngeal crowding, as evaluated by the MS, are unlikely to respond to oral appliance treatment.

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Author contributions: Dr Tsuiki had full access to all of the data in the study and takes responsibility for the integrity of the data and accuracy of the data analysis.
Dr Tsuiki: contributed to conception, study design, data collection, interpretation of data, and manuscript drafting.
Dr Ito: contributed to data collection, data analysis, interpretation of data, and writing of the manuscript.
Dr Isono: contributed to conception and interpretation of data and writing and revision of the manuscript.
Dr Ryan: contributed to conception and interpretation of data and writing of the manuscript.
Dr Komada: contributed to data analysis and revision of the manuscript.
Dr Matsuura: contributed to data analysis and writing of the manuscript.
Dr Inoue: contributed to conception, interpretation of data, and manuscript drafting.

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