

# Journal of Dental Sleep Medicine

Official Publication of the American Academy of Dental Sleep Medicine | [www.jdsm.org](http://www.jdsm.org)

**Volume 3, Number 2**

**April 10, 2016**

**Pages 37–76**

---

## *In This Issue*

**Patient Communities and Personalizing  
Sleep Medicine: MyApnea.Org**  
*Kontos and Redline*

**Treatment of Obstructive Sleep Apnea with  
a Tongue-Stabilizing Device at a Single  
Multidisciplinary Sleep Center**  
*Yanagihara, Tsuiki, Setoguchi, Inoue*

**Maxillomandibular Advancement Surgery  
as a Treatment of Obstructive Sleep Apnea  
in a Patient with Cleidocranial Dysostosis:  
A Case Report**  
*Chance and Pollan*

**A Case of Polysomnographic Changes Using  
a Twin-Block Appliance in a Child with  
Maxillary Protrusion**  
*Hosoya, Hitoshi, Kazunori*

---







Official Publication of the American  
Academy of Dental Sleep Medicine

# Journal of Dental Sleep Medicine

Volume 3, Number 2 | April 10, 2016 | Pages 37–76

## Editor-in-Chief

Leslie Dort, DDS

## Deputy Editor

Olivier Vanderveken, MD, PhD

## Associate Editors

Fernanda Almeida, DDS, PhD

Gilles Lavigne, DMD, PhD

Rose Sheats, DMD

## Executive Director

Jerome A. Barrett

## Managing Editor

Andrew Miller

## Editorial Board

Ghizlane Aarab, DDS, PhD

Peter Cistulli, MD, PhD

Greg Essick, DDS, PhD

Bernard Fleury, MD

Nelly Huynh, PhD

Sam Kuna, MD

Chris Lettieri, MD

Frank Lobbezoo, DDS, PhD

Alan Lowe, DMD, PhD

Marie Marklund, DDS, PhD

Jean-Francois Masse, DMD, MSc

Antonio Romero-Garcia, DDS, PhD

Kate Sutherland, BSc(Hons), PhD

Satoru Tsuiki, DDS, PhD

*Journal of Dental Sleep Medicine (JDSM)* (Online 2333-9756; Website: [www.jdsm.org](http://www.jdsm.org)) is published online quarterly on the 10<sup>th</sup> of January, April, July and October by the American Academy of Dental Sleep Medicine, 2510 North Frontage Road, Darien, IL 60561-1511, phone (630) 737-9705 and fax (630) 737-9790.

**ADVERTISING:** Digital advertising is available on [www.jdsm.org](http://www.jdsm.org). Please contact the National Sales Account Executive at [advertising@asmnet.org](mailto:advertising@asmnet.org) for complete information.

**PERMISSION TO REPRODUCE:** Written permission to reproduce, in print or electronically,

whole articles or any parts of works, figures or tables published in *JDSM* must be obtained prior to publication. Permission for republication must be arranged through the Copyright Clearance Center, Inc., 222 Rosewood Drive, Danvers, MA 01923, phone (978) 750-8400 or fax (978) 646-8600 or URL <http://www.copyright.com>. There are royalty fees associated with such permissions.

**REPRINTS:** For author reprints contact the AADSM office. For commercial reprint orders contact Cenveo Publisher Services, 4810 Williamsburg Road, #2, Hurllock, MD 21643 or [Reprints2@cadmus.com](mailto:Reprints2@cadmus.com).

**DISCLAIMER:** The statements and opinions contained in editorials and articles in this journal are solely those of the authors thereof and not of the American Academy of Dental Sleep Medicine, or of its officers, regents, members or employees. The Editor-in-Chief, the American Academy of Dental Sleep Medicine and its officers, regents, members and employees disclaim all responsibility for any injury to persons or property resulting from any ideas or products referred to in articles contained in this journal.

© 2016 American Academy of Dental Sleep Medicine

---

**EDITORIALS**

**39**

**What is Success?**

Leslie C. Dort

**41**

**Patient Communities and Personalizing Sleep  
Medicine: MyApnea.Org**

Emily Kontos, Susan Redline

---

**ORIGINAL ARTICLES**

**43**

**Treatment of Obstructive Sleep Apnea with  
a Tongue-Stabilizing Device at a Single  
Multidisciplinary Sleep Center**

Mariko Yanagihara, Satoru Tsuiki, Yasuhiro Setoguchi,  
Yuichi Inoue

---

**REVIEW ARTICLES**

**49**

**Health-Related Quality of Life Assessment Tools  
and Sleep-Disordered Breathing**

Rose D. Sheats

**57**

**Skeletal Malocclusion and Genetic Expression: An  
Evidence-Based Review**

Clarice Nishio, Nelly Huynh

---

**CASE REPORTS**

**65**

**Maxillomandibular Advancement Surgery as a  
Treatment of Obstructive Sleep Apnea in a Patient  
with Cleidocranial Dysostosis: A Case Report**

Heather Chance, Lee Pollan

**71**

**A Case of Polysomnographic Changes Using a  
Twin-Block Appliance in a Child with Maxillary  
Protrusion**

Hisashi Hosoya, Kawanabe Hitoshi, Fukui Kazunori

**73**

**A Pitfall of an Orthodontic Approach to Pubescent  
Obstructive Sleep Apnea: A Case Report**

Keiko Maeda, Eiki Itoh, Yoko Okawara, Yoichiro Takei,  
Mina Kobayashi, Yuichi Inoue, Satoru Tsuiki

---

**NEWS AND UPDATES**

**75**

**AADSM 2016 Educational Calendar of Events**

AADSM Staff

# What is Success?

Leslie C. Dort, DDS, Diplomate, ABDSM, Editor-in-Chief *Journal of Dental Sleep Medicine*

Calgary, Alberta, Canada

During a recent webinar discussing the latest AASM/AADSM clinical practice guideline for the treatment of obstructive sleep apnea (OSA) with oral appliances (OAs) a participant asked whether the guideline defined what is considered treatment success with oral appliance therapy. This question has a number of answers depending on where OA therapy is placed in the treatment recommendations for OSA. If OAs are to be considered for all severities then evidence suggesting outcomes equivalent to other treatments, primarily CPAP, is required. Does that evidence exist? What about the question, “What is the definition of CPAP success?” Perhaps it is best to begin with the broader questions “What is quality care for adults with OSA?” and “Can OA therapy provide quality care for OSA?”

The recent publication, “Quality Measures for the Care of Adult Patients with Obstructive Sleep Apnea”<sup>1</sup> identified three outcomes to be applied and assessed in order to improve the quality of life and cardiovascular outcomes for individuals with OSA as well as increase public safety. The three measures were: (1) improve disease detection and categorization; (2) improve quality of life; and (3) reduce cardiovascular risk.

The first measure, disease detection and categorization, requires multi-disciplinary collaboration so the dental sleep medicine clinician has an accurate diagnosis and starting point to therapy.

The second and third measures address treatment issues whereby quality care is more likely to lead to “successful” care. Is OA therapy likely to lead to improvement in quality of life? The verdict is in. The meta-analysis conducted as part of the recent guideline states that “OAs are nearly equivalent to CPAP for improving QOL in adult patients with OSA.”<sup>2</sup> For an introduction to quality of life measurement and tools (questionnaires) see the article by Sheats<sup>3</sup> in this issue.

Are OAs likely to reduce cardiovascular risk compared to CPAP? The quality measure suggested by Aurora et al.<sup>1</sup> is assessment of blood pressure. Two recent comprehensive meta-analyses have yielded very similar results: OAs are equivalent<sup>4</sup> or nearly equivalent<sup>2</sup> to CPAP in reducing blood pressure in adults with OSA.

Overall if quality of life and blood pressure outcomes are equivalent when patients are pooled together in meta-analyses does it make sense to say that CPAP is more effective than OAs?

What about the individual patient? Medical sleep specialists (clinical experience of myself and colleagues) continue to say that because CPAP is better than OAs at reducing AHI, it should be the treatment of first choice. What does the evidence say? The recent guideline found that CPAP reduced AHI more than OAs by a mean of 6.24 events/h (95% CI: 8.14, 4.34).<sup>2</sup> Is a reduction of AHI of 6.24 events/h clinically significant?

The successful treatment of an individual with OSA is not a number such as AHI < 5, or < 10. It is a combination of outcomes and ongoing assessment. Hopefully, in the field of sleep disordered breathing we can move beyond the number and work towards a patient centered and patient relevant definition of success.

## CITATION

Dort LC. What is success? *Journal of Dental Sleep Medicine* 2016;3(2):39.

## REFERENCES

1. Aurora RN, Collop NA, Jacobowitz O, Thomas SM, Quan SF, Aronsky AJ. Quality measures for the care of adult patients with obstructive sleep apnea. *J Clin Sleep Med* 2015;11:357–83.
2. Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *Journal of Dental Sleep Medicine* 2015;2:71–125
3. Sheats R. Health-related quality of life assessment tools and sleep disordered breathing. *Journal of Dental Sleep Medicine* 2016;3:49–55.
4. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. *JAMA* 2015;314:2280–93.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2016

Accepted for publication March, 2016

Address correspondence to: Leslie C. Dort, DDS, 1016-68th Ave SW, Suite 150, Calgary, AB T2V 4J2, Canada; Tel: (403) 202-4905; Fax: (403)202-0266; Email: lcdort@gmail.com

## DISCLOSURE STATEMENT

Dr. Dort is Editor-in-Chief of *Journal of Dental Sleep Medicine*.



# Patient Communities and Personalizing Sleep Medicine: MyApnea.Org

Emily Kontos, ScD, ScM; Susan Redline, MD, MPH

*Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

A new web-based community portal, [www.MyApnea.Org](http://www.MyApnea.Org), is mobilizing a community of patients, researchers and health care providers to work together to identify better ways to screen, treat, and prevent sleep apnea. *MyApnea.Org* is the public face of the Sleep Apnea Patient Centered Outcomes Network (SAPCON), a patient-powered research network that was formed to improve comparative effectiveness research by focusing on patient-centered outcomes. This type of research asks: *Of available treatment alternatives, which treatments are most effective, and for which patients?*

There has never been a more urgent time in sleep medicine and oral health for patient and stakeholder participation in such a national comparative effectiveness research initiative. With escalating health care costs, payers are demanding higher levels of evidence to justify the use of diagnostic tests and treatments and are asking for data that provides value to the patient and health care system. Many insurers restrict how sleep tests and treatments are delivered; however, those requirements often reflect a generalization of data from studies that were conducted at highly specialized referral centers and were not intended to be used without the support of a full team of committed sleep health professionals.

The need for comparative effectiveness and patient-centered research is especially relevant for Dental Sleep Medicine. For example, there is growing evidence that mandibular advancement devices (MADs) play an important role in the management of patients with sleep apnea. However, there remain critical questions on which patients benefit the most from this treatment, and when this treatment should be offered in the course of sleep apnea management. Answers to those questions require data on large numbers of well-characterized patients, allowing for both subgroup and prospective analyses. Although recent research has shown equivalent blood pressure improvement with use of MADs compared to CPAP, it is clear that patient-reported outcomes, including improvement in sleepiness, fatigue, and sleep quality, as well as overall satisfaction with treatment, are important outcomes for patients as well as for health care systems. Developing the evidentiary base for health care decisions will require that careful consideration of the cost-benefit of alternative treatments, including impact on health outcomes and quality of life.

Patients commonly express frustration over the lack of sleep apnea treatment options, especially the paucity of information that addresses which options would work best for them. Patients also often find that their treatment may be influenced by which specialist they happen to see, rather than information on their own set of risk factors or personal preferences. Finally, patients often are disappointed by the level of support available

to aid them in understanding how to adjust to given treatments or to overcome barriers. They are often interested in learning technical and behavioral tips that allow them to better use their prescribed devices and to follow healthier sleep routines, and be further supported by trusted peers. For these reasons, patients are increasingly looking to form communities where they can access and share information, support one another, connect to dedicated professionals, and also contribute data to advance everyone's understanding of sleep apnea.

In response to these needs and opportunities, *MyApnea.Org* is inviting people with (or at-risk of) sleep apnea to share information, provide support, and to help design, direct, and participate in sleep research. A broad and collaborative effort is what is needed to generate the evidence necessary for deciding which diagnostic studies and treatments are most effective. Studies of large numbers of individuals from across the US (and the world) are needed to achieve the sample sizes necessary for identifying which patients benefit most (or might be harmed) from alternative sleep apnea treatments, such as MADs. Rather than the traditional "one size fits all" approach to treatments and research, *MyApnea.Org* hopes to use information on health risk factors, biomarkers, background, and type of sleep apnea to tailor treatments that are likely to be most effective for individual patients. In such a way, data will be generated to allow a patient with a given set of risk factors (based on airway size, body fat distribution, time in REM sleep, etc.) to be offered treatments most likely to benefit him or her. Furthermore, research that addresses the outcomes that matter to patients (e.g., fatigue in women, behavioral problems in children) will ensure that the results are relevant and would improve the health and well-being of patients with sleep apnea. It is also an exciting time in sleep research as technological advances currently present numerous opportunities for improving sleep apnea diagnosis and management. Examples include telemedicine, newer ambulatory monitoring devices, mHealth devices, and sophisticated oral appliances and pressure devices. However, without good evidence on what works best, such technologies can be misused. *MyApnea.Org* is building a platform to conduct such large-scale patient-driven comparative effectiveness research.

Patient members of *MyApnea.Org* have the opportunity to complete a series of health related surveys, nominate, and vote on research questions and can participate in forums to discuss how patient-centered research should be conducted. After completing the patient reported outcomes surveys, patients are able to see their answers in comparison with the rest of the patient community. Through these research communities patients can identify what questions are most important

and can co-develop proposals with health care and oral health providers and scientists to address these needs. To date, over 3,000 members have contributed patient reported outcomes survey data and members have identified 54 research topics that over 3,000 members have endorsed.

The empowering strength of MyApnea.Org lies in the breadth and diversity of its membership. MyApnea.Org already has enrolled over 6,700 members and will soon begin enrollment of parents of children with sleep apnea. The portal attracts more than 1,000 new visitors a day and sees over 25,000 page views a month. MyApnea.Org maintains high retention rates, with 60% of our visitors returning within a week and over 80% returning within a month. Members come from every state in the U.S. as well as 41 countries world-wide. The forum provides a vibrant and engaged patient community with over 1,500 current posts on 190 different topics. Topics span a wide range of topics. For example, the thread on oral appliances has had over 1,600 views. In addition, there have been extensive discussions related to sinus issues and sleep apnea and the need for appropriate oral appliances. A consistent theme throughout the discussion forum is the desire for alternative treatments to mainline therapies such as CPAP. Many patients are not fully aware of the array of treatment modalities that may be available to them. Participation in MyApnea.Org and communication with other patients and providers offers them the opportunity to learn more not only to help direct future research but to also better empower the management of their own health care.

Sleep researchers and providers are also encouraged to join MyApnea.Org. After becoming a member, providers are prompted to create their own specific landing page with a unique web address and welcome message for their patients. These personalized web links enable providers to promote the site among their patient panel and when patients register for the site using the personalized link, providers and patients are connected within the MyApnea.Org database. Once a provider has at least 20 patients registered for the site they are able to view the aggregate patient reported outcomes for their patient panel and compare results against the entire patient community.

The key message to pass along to dental health patients is that it is now easier than ever for patients with sleep apnea to play an active role not only their health care but in the research that is driving the decisions behind their health care. This is ever so important in the area of sleep health where the persisting gaps in knowledge are a significant deterrent to equitable health. MyApnea.Org, already has enrolled more than 6,700 members in this national effort. We encourage dental clinicians to refer patients with sleep apnea to join the patient-powered research network MyApnea.Org and to remind them that their data has the power to move the dial in sleep health. Similarly, we encourage dental clinicians and researchers to consider using the data provided within MyApnea.Org for future investigations. As further comparative effectiveness research is generated, dental practitioners and researchers will have a better understanding of which patients benefit from mandibular devices and how best to screen and manage a wide array of patients.

## CITATION

Kontos E, Redline S. Patient communities and personalizing sleep medicine: MyApnea.Org. *Journal of Dental Sleep Medicine* 2016;3(2):41–42.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2015

Accepted for publication January, 2016

Address correspondence to: Susan Redline, MD, Harvard Medical School, Department of Medicine and Division of Sleep Medicine, Brigham and Women's Hospital and Beth Israel Deaconess Medical Center, 221 Longwood Avenue, Room 225, Boston, MA 02115; Tel: (617) 732-4013; Fax: (617) 732-4015; Email: sredline@partners.org

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.



# Treatment of Obstructive Sleep Apnea with a Tongue-Stabilizing Device at a Single Multidisciplinary Sleep Center

Mariko Yanagihara, MD<sup>1,2,3</sup>; Satoru Tsuiki, PhD<sup>1,2,4</sup>; Yasuhiro Setoguchi, PhD<sup>3</sup>; Yuichi Inoue, PhD<sup>1,2,4</sup>

<sup>1</sup>Institute of Neuropsychiatry, Tokyo, Japan; <sup>2</sup>Foundation of Sleep and Health Sciences, Tokyo, Japan; <sup>3</sup>Department of Respiratory Medicine, Tokyo Medical University, Tokyo, Japan; <sup>4</sup>Department of Somnology, Tokyo Medical University, Tokyo, Japan

**STUDY OBJECTIVES:** Mandibular advancement devices (MADs) may not be acceptable for use in patients with obstructive sleep apnea (OSA) when dental and/or temporomandibular joint side effects are likely. Tongue-stabilizing devices (TSDs) are a potential alternative to MAD therapy. We aimed to document the outcome of TSD treatment at a single multidisciplinary sleep center.

**METHODS:** OSA patients for whom MAD treatment was contraindicated due to dental and/or temporomandibular joint problems were prescribed a TSD. Follow-up overnight polysomnography (PSG) was performed with a TSD in place. Responders were defined as patients with a reduction in the apnea-hypopnea index (AHI) to less than 5 events/h as well as more than a 50% reduction in baseline AHI.

**RESULTS:** Of 551 patients who were referred for oral appliance therapy, 76 (100%) were prescribed a TSD. There were patients who were acclimatizing to TSD (n = 6; 8%), intolerant (n = 22; 29%), lost to follow-up (n = 26; 34%), and stopped using TSD by other reasons (n = 6; 8%). Of the 16 subjects (21%) who completed follow-up testing of PSG, the mean baseline AHI was reduced from  $21.8 \pm 8.6$  to  $9.3 \pm 5.8$  events/h ( $p < 0.01$ ) with a TSD in place. The TSD improved AHI from  $14.2 \pm 2.9$  to  $2.1 \pm 1.3$  events/h in 5 responders (7%) ( $p < 0.01$ ).

**CONCLUSIONS:** The efficacy of the TSD was similar to that reported for MADs as long as the TSD was tolerated, especially in mild OSA patients. However, the high percentage of treatment dropout and/or lost to follow-up suggests the potential need for appliance redesign or modification to improve patients' adherence to therapy.

**KEYWORDS:** obstructive sleep apnea, oral appliance, tongue-stabilizing device

**CITATION:** Yanagihara M, Tsuiki S, Setoguchi Y, Inoue Y. Treatment of obstructive sleep apnea with a tongue-stabilizing device at a single multidisciplinary sleep center. *Journal of Dental Sleep Medicine* 2016;3(2):43–47.

## INTRODUCTION

Obstructive sleep apnea (OSA) is a major public health problem that has been associated with long-term adverse health consequences including hypertension, metabolic dysfunction, and cardiovascular disease.<sup>1</sup> Nasal continuous positive airway pressure (nCPAP) has been the standard treatment for OSA for more than three decades,<sup>2</sup> while oral appliances (mandibular advancement devices [MADs]) and tongue-retaining devices have been prescribed for patients with mild to moderate OSA and/or who fail to use nCPAP.<sup>3,4</sup> In clinical settings, both sleep dentists and physicians often encounter patients for whom MADs are contraindicated even for mild OSA and nCPAP failure due to compromised dentition, severe periodontal disease, or temporomandibular joint disorders.<sup>4</sup>

A tongue-retaining device that maintains the tongue in a protruding position by suction was first documented by Cartwright and Samelson in 1982.<sup>5</sup> The device can be recommended for OSA patients when MADs are contraindicated, although these devices are generally less common and less efficacious than MADs.<sup>6–8</sup> A tongue-stabilizing device (TSD) is a type of tongue-retaining device that is now commercially available (Aveo-TSD, Innovative Health Technologies, New Zealand) (Figure 1).<sup>9–11</sup> The great differences between the earlier design of the tongue-retaining device reported in 1982 and the TSD are their design and fabrication. The tongue-retaining device is custom made from dental casts since the appliance entirely covers the upper and lower dental arches for appliance retention. Conversely,

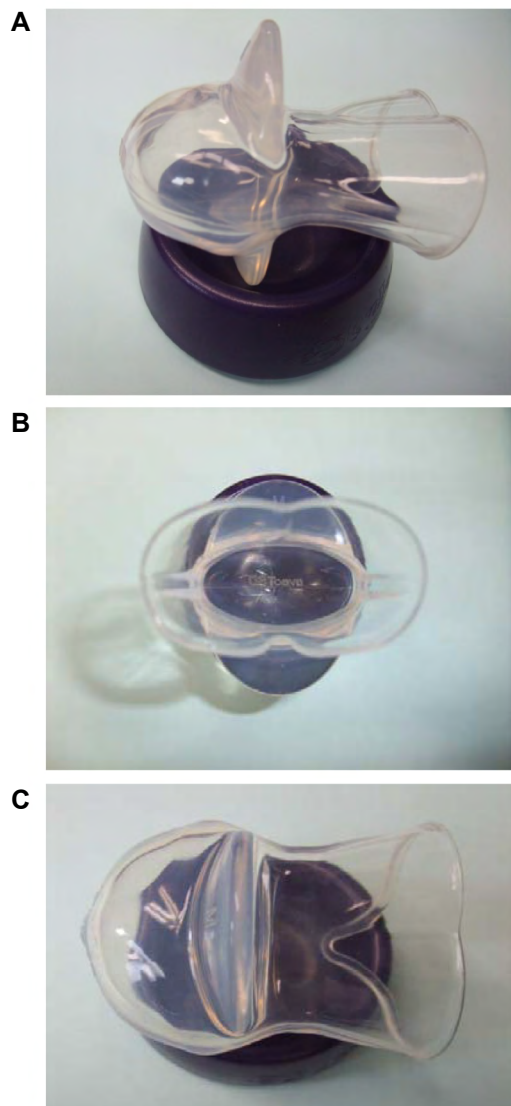
TSD is a preformed silicone appliance without dental coverage but still has the anterior bulb being retained in place only by tongue suction.<sup>9,10</sup> Therefore, patients need no dental impression undertaken for TSD fabrication; it could be assumed that TSD has succeeded in reducing bulk in comparison with the original tongue-retaining device. Because of this simplicity, TSD was used to prevent snoring at temporary refuges after the earthquake and nuclear power plant accident in Japan in 2011.<sup>11</sup>

Several studies have demonstrated that the TSD is as efficacious as a titratable oral appliance for improving OSA.<sup>9,10</sup> The results of research and the advantage of its simplicity in the field suggest that the TSD may be underused in the treatment of OSA. However, to date, there have been no observational reports on its prescription, effectiveness, or tolerance in a clinical setting. The purpose of this study was to document patient flow and the outcome of TSD treatment at a single multidisciplinary sleep center. This is the first report of TSD use in a clinical setting.

## METHODS

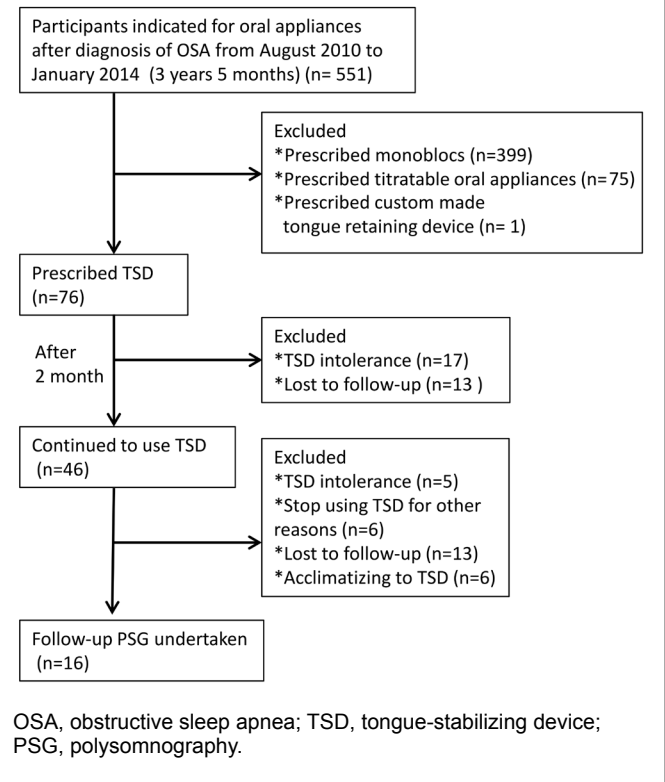
### Patients

The protocol of this investigation was approved by the ethics committee of the Foundation of Sleep and Health Sciences, Tokyo, Japan. Figure 2 shows the flow of participants. The prospective recruitment of eligible patients was conducted over a period of 41 months (3 years 5 months) from August 2010, when the first TSD was prescribed at the Yoyogi Sleep Disorder Center, Tokyo,

**Figure 1**—Tongue-stabilizing device (TSD).

The TSD is a translucent, preformed silicon appliance (A). It is composed of three parts: a tongue holder (the lumen of the TSD), a negative pressure generator (a bulb at the tip of the socket), and two flanges (upper and lower parts of the socket). The tongue is inserted from this position (B). The frenulum of tongue is placed in a small notch in the bottom of the TSD (C) and the flanges are placed in front of the upper and lower lips. See also Deane et al.<sup>9</sup> for details.

to January 2014. Patients who were indicated for oral appliance therapy after a diagnosis of OSA ( $n = 551$ ) were referred to the sleep apnea dental clinic at the Yoyogi Sleep Disorder Center. This patient recruitment was also performed consecutively. Inclusion criteria were: Japanese of both genders who were diagnosed with OSA (apnea-hypopnea index [AHI] > 5 events/h) by initial overnight polysomnography (PSG) performed at the center; OSA patients for whom MADs were contraindicated because of severe periodontitis, insufficient number of teeth, denture use, and/or temporomandibular joint dysfunction. Both mild-to-moderate OSA patients who did not require nCPAP and moderate-to-severe OSA patients who failed to use nCPAP were included. Patients who met one or more of the following exclusion criteria

**Figure 2**—Flowchart of participants.

were excluded: severe cardiovascular disease, medically complicated, or medically unstable. Patients who were prescribed monoblocs (ASO International, Tokyo, Japan) ( $n = 399$ ), titratable oral appliances (SomnoDent, SomnoMed Japan, Japan) ( $n = 75$ ), or custom-made tongue-retaining devices (ASO International, Tokyo, Japan) ( $n = 1$ ) were also excluded.<sup>12,13</sup> Consequently, 76 patients were prescribed a TSD during the study period. All of these patients agreed that their PSG results could be used for research purposes, and provided written informed consent with respect to the anonymous use of their data.<sup>13</sup>

### Polysomnographic Evaluation

Episodes of hypopnea were determined based on the American Academy of Sleep Medicine criteria of a reduction in airflow amplitude  $\geq 50\%$  from baseline persisting for  $\geq 10$  s, or some level of reduction in airflow amplitude persisting  $\geq 10$  s with the presence of respiratory-associated arousal and/or oxygen desaturation  $\geq 3\%$  (Chicago criteria).<sup>14</sup> The severity of OSA was assessed in terms of AHI (mild [AHI  $\geq 5$  to < 15 events/h], moderate [AHI  $\geq 15$  to < 30 events/h], and severe [AHI  $\geq 30$  events/h]).

### Tongue-Stabilizing Device

Detailed information on the TSD and its indications have been reported previously.<sup>9,10</sup> Briefly, the tongue is inserted into the anterior bulb and sucked by the negative pressure generated by squeezing the bulb. Potential risks of the TSD include soreness and/or discomfort of the tongue, excessive saliva or dry mouth, and discomfort of the lips, teeth, and gums.<sup>9,10</sup> Use of a TSD is associated with minimal side effects in the temporomandibular joint.

**Table 1**—Effects of a tongue-stabilizing device on polysomnographic parameters in 16 OSA patients.

	Baseline	With TSD	p value
AHI (events/h)	21.8 ± 8.6	9.3 ± 5.8**	< 0.01
3%ODI (events/h)	17.9 ± 7.6	7.8 ± 5.6**	< 0.01
SpO <sub>2</sub> < 90% (%)	0.23 ± 0.22	0.42 ± 0.48	ns
Nadir SpO <sub>2</sub> (%)	85.6 ± 3.8	87.9 ± 5.1	ns
Arousal index (events/h)	19.0 ± 5.8	13.9 ± 6.5	ns
Respiratory event-related arousal index (events/h)	10.7 ± 6.5	3.8 ± 2.7**	< 0.01

Values are expressed as the mean ± standard deviation. \*\*p < 0.01 versus baseline. TSD, tongue-stabilizing device; AHI, apnea-hypopnea index; 3%ODI, 3% oxygen desaturation index; SpO<sub>2</sub> < 90%, percentage of the total sleep time spent with percutaneous oxygen saturation less than 90%; arousal index, respiratory event-related arousals and other arousals.

### Protocol and Treatment Outcome

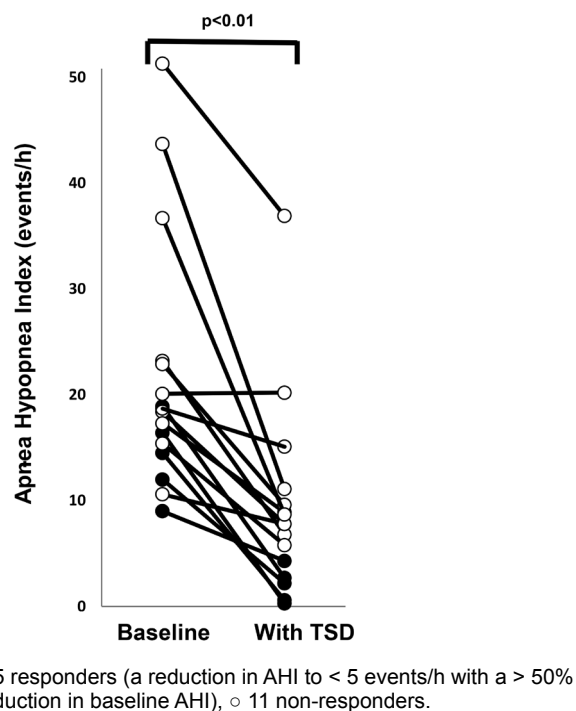
A TSD was prescribed after the methods were explained in detail. Patients were advised to increase the suction level as necessary to maintain sufficient retention, or to decrease suction if they felt excessive discomfort on their tongue. A second overnight PSG was undertaken with the TSD in place when patients had used the TSD regularly and experienced subjective improvements in OSA symptoms, such as with regard to snoring, morning headache, or sleep quality. Changes in daytime sleepiness were evaluated with the Japanese version of the Epworth Sleepiness Scale (JESS).<sup>15</sup> Responders to TSD treatment were defined as patients who showed a reduction in AHI to < 5 events/h with a > 50% reduction in baseline AHI.<sup>12</sup>

### Statistical Analysis

The normality of the data distribution was assessed using the Kolmogorov-Smirnov test. Paired t-tests were used to compare the differences in PSG variables between baseline and follow-up, whereas unpaired t-tests were used to compare the difference in each PSG variable between responders and non-responders. Sensitivity, specificity, and positive and negative predictive values were also assessed based on a 2 × 2 cross table that was used to investigate the effect of baseline AHI on the responder-nonresponder distribution. Finally, in order to describe any differences in those patients who continued and who discontinued treatment (excluding subjects who were lost to follow-up), a univariate logistic regression followed by a multivariate logistic regression analysis was performed to investigate contributions to the likelihood of continuation of TSD therapy by incorporating gender, age, JESS, BMI, and baseline AHI. A p value of < 0.05 was considered to be statistically significant.

## RESULTS

A total of 76 subjects were prescribed a TSD (**Figure 2**). Thirty patients dropped out of TSD treatment within 2 months. Of these 30 subjects, 17 patients complained of tongue soreness and/or dry mouth and/or increased salivation and/or disturbed sleep due to irritation of the tongue and soft tissues. All 17 patients also complained that TSD came off easily. The remaining 13 patients were lost to follow-up. After 2 months, 5 patients dropped out because of the same reasons as the above 17 patients. Six patients stopped using TSD because of falling off (n = 3), appliance broken (n = 1), dental treatment required (n = 1), and decease (n = 1). In addition, there

**Figure 3**—Effects of the tongue-stabilizing device (TSD) on the severity of OSA.

were 13 patients lost to follow-up and 6 patients who were acclimatizing to TSD.

Sixteen of the 76 OSA patients (7 males and 9 females) completed a follow-up PSG with a TSD in place (**Table 1**). The mean ± standard deviation (SD) of age, BMI, and JESS at baseline in these 16 patients were 63.6 ± 9.2 years, 24.0 ± 2.9 kg/m<sup>2</sup>, and 12.0 ± 5.3 points, compared to 64.6 ± 9.2 years, 24.1 ± 3.0 kg/m<sup>2</sup>, and 9.8 ± 4.8 points at follow-up PSG with a TSD in place. There were no significant changes in BMI or JESS throughout the study. TSD significantly reduced AHI (p < 0.01), 3% oxygen desaturation index (3%ODI) (p < 0.01), and respiratory event-related arousal index (p < 0.01), while no significant changes were seen in the percentage of total sleep time spent with percutaneous oxygen saturation less than 90% (SpO<sub>2</sub> < 90%), nadir SpO<sub>2</sub>, and arousal index (**Figure 3**).

Among the 16 patients who completed a follow-up PSG with a TSD in place, there were 5 responders (31.3%) and 11

**Table 2**—Comparison of each parameter between responders and non-responders to TSD.

	Responder (n = 5)		Non-responder (n = 11)	
	Baseline	With TSD	Baseline	With TSD
Age (y)	61.0 ± 8.4	61.8 ± 8.3	64.7 ± 9.8	65.8 ± 9.7
BMI (kg/m <sup>2</sup> )	24.9 ± 3.2	24.7 ± 3.3	23.6 ± 2.7	23.8 ± 2.9
JESS (score)	15.2 ± 5.0	13.2 ± 7.0	10.5 ± 4.0	8.2 ± 3.1
AHI (events/h)	14.2 ± 2.9	2.1 ± 1.3**	25.3 ± 10.1††	12.6 ± 6.2**
3%ODI (events/h)	11.0 ± 4.8	2.2 ± 1.6*	21.0 ± 8.6	10.4 ± 6.5**
SpO <sub>2</sub> < 90% (%)	0.27 ± 0.22	0.00 ± 0.00	0.21 ± 0.21	0.61 ± 0.54
Nadir SpO <sub>2</sub> (%)	84.2 ± 3.7	93.0 ± 1.6*	86.3 ± 3.9	85.5 ± 4.5
Arousal index (events/h)	17.2 ± 4.5	9.1 ± 1.8	19.9 ± 5.9	16.1 ± 7.7
Respiratory event-related arousal index (events/h)	6.6 ± 4.0	1.0 ± 0.9	12.6 ± 6.9	5.0 ± 3.0*

Values are expressed as the mean ± standard deviation. \*p < 0.05 versus baseline. \*\*p < 0.01 versus baseline. ††p < 0.05 versus responder. BMI, body mass index; JESS, Japanese version of the Epworth Sleepiness Scale.<sup>14</sup> Other abbreviations are the same as in Table 1.

**Table 3**—Use of a cut off baseline apnea-hypopnea index for predicting the outcome of treatment with the tongue-stabilizing device.

	Responders	Non-responders	Total
Baseline AHI < 15	3	1	4
Baseline AHI ≥ 15	2	10	12
Total	5	11	16

The AHI cut-off was set at 15 events/h. Abbreviations are the same as those in Table 1. Sensitivity = 0.60, Specificity = 0.90, Positive predictive value = 0.75, Negative predictive value = 0.83.

non-responders (Table 2). Among the responders, TSD treatment reduced 3%ODI from 11.0% ± 4.8% to 2.2% ± 1.6% (p = 0.04) and increased the nadir SpO<sub>2</sub> value from 84.2% ± 3.7% to 93.0% ± 1.6% (p = 0.03). No significant changes were found in the arousal index or the respiratory arousal index. In non-responders, TSD reduced AHI (p < 0.01), 3%ODI (p < 0.01), and the respiratory arousal index (p = 0.02). Moreover, the mean baseline AHI of non-responders (AHI = 25.3 ± 10.1 events/h) was significantly higher than that of responders (AHI = 14.2 ± 2.9 events/h) (p = 0.02).

When the 16 patients were divided into a mild OSA group (baseline AHI < 15) and a moderate to severe OSA group (baseline AHI > 15 events/h), this cutoff value gave a sensitivity/specificity and positive predictive value/negative predictive values of 0.60/0.90 and 0.75/0.83, respectively. Accordingly, 3 of 4 (75%) patients with mild OSA responded whereas only 2 of 12 (17%) patients with moderate to severe OSA responded to TSD.

A univariate logistic regression analysis revealed that continuation of TSD treatment was not associated with gender (odds ratio [95% confidence interval]) (0.417 [0.095–1.830], p = 0.417), age (1.023 [0.951–1.101], p = 0.536), BMI (1.002 [0.791–1.271], p = 0.986), JESS (1.076 [0.927–1.249], p = 0.337), and baseline AHI (1.049 [0.973–1.132], p = 0.210). No significant observation was also found when multivariate logistic regression analysis was applied (data not shown).

## DISCUSSION

This is the first report to document TSD use in a single multidisciplinary sleep center. Of the 16 subjects who completed the protocol, only 5 patients had an AHI on TSD treatment that met criteria for an acceptable response used in previous reports.<sup>12,13</sup>

The treatment success rate with MADs has been reported to range from 19% to 57% when treatment success was defined as follow-up AHI < 5 events/h.<sup>4</sup> In 16 patients who completed follow-up PSG with TSD in place, the treatment success rate with a TSD was 31%, which was slightly better than the 22.7% reported by Deane et al.<sup>9</sup> under the same responder criterion. Therefore, we speculate that TSD could also be recommended for OSA patients for whom MADs are indicated. Lazard et al.<sup>7</sup> reported that the conventional tongue-retaining device provided a complete success (post-treatment AHI < 10) rate of 47% and a partial response (10 < follow-up AHI < 20 with > 50% reduction from baseline AHI) rate of 24%. Under the same definition of responder as Lazard et al.,<sup>6</sup> the complete and partial response rates in our study were 75% and 12.5%, respectively. A balanced combination of positive predictive value and negative predictive value of 0.75/0.83 supports the notion that a TSD is efficacious, although the number of total subjects was limited.

By contrast, to authors' surprise, only 16 of 76 TSD users (21%) managed to complete the follow-up PSG with a TSD. Furthermore, based on the total number of 76 patients, only 7% (5 responders) had a successful outcome. We were greatly disappointed that 34% (26/76) of TSD users were gradually lost to follow-up and 29% (22/76) did not tolerate the appliance, although all of the patients were encouraged to regularly visit the outpatient clinic after appliance prescription. Since an additional logistic regression analysis demonstrated that continuation of TSD treatment was not associated with gender, age, JESS, BMI, and the severity of OSA at baseline, we speculate that the lower adherence may be due to the side effects, which included excess salivation, dryness of the mouth, and irritation of the tongue and soft tissues. These side effects have been previously reported by Deane et al.<sup>8,9</sup> Dort and Brant reported that 45%



of users indicated that they would continue treatment with a tongue-retaining device because their snoring was reduced.<sup>6</sup> While a TSD was likely to benefit OSA patients based on a balanced positive predictive value and negative predict value in this study (Table 3), an unexpectedly higher percentage of intolerance and lost to follow-up within 2 months could be related to an attenuated risk-benefit profile. Therefore, modification of the appliance design to decrease subjective symptoms and discomfort of the tongue may be needed, while retaining the simplicity of the design. A TSD should still be considered in the treatment of OSA for individuals who cannot use either nCPAP or MADs.

Pathophysiologically, the velopharynx is the major site of occlusion in patients with OSA.<sup>16</sup> A previous report demonstrated that a TSD improved velopharyngeal airway patency by a ventral displacement of the tongue.<sup>10</sup> Since simple tongue stabilization at a protruded position appears to produce ventral traction of the soft palate, even without mandibular advancement,<sup>17</sup> the connection between the tongue and the soft palate via the palatoglossus muscle could contribute to the favorable response. To increase the retention of the tongue in a protruded position, Dort and Brant attempted to narrow the base of the tongue bulb and succeeded in improving the respiratory disturbance index in OSA patients.<sup>5</sup> Dort and Remmers<sup>17</sup> further suggested that the efficacy of treatment improved when an anterior bulb was incorporated into a mandibular advancing splint. Tsuiki et al.<sup>19</sup> recently reported that holding the tongue in position would likely alleviate dorsal displacement of the tongue while sleeping in a severe OSA patient without protruding the tongue. Thus, an approach that focuses on controlling the tongue in position, rather than tongue protrusion, could be meritorious in oral appliance therapy while avoiding (1) the common dental/temporomandibular joint side effects frequently seen with the use of MADs and (2) the irritation/soreness of the tongue in TSD therapy, leading to improving patients' adherence.

In conclusion, we have documented the outcome of TSD use in a single multidisciplinary sleep center. A TSD can be as efficacious as mandibular advancing splints, especially in patients with mild OSA, if they can tolerate the device. The high percentage of dropouts and/or loss to follow-up suggests that redesign or modification of the TSD design may be necessary to improve patients' adherence to therapy.

## REFERENCES

- Chan AS, Lee RW, Lavigne GJ, Cistulli PA. Pathophysiology of obstructive sleep apnea. In: Lavigne GJ, Cistulli PA, Smith MT, eds. *Sleep medicine for dentists: a practical overview*. Illinois: Quintessence Publishing Co, Inc, 2009:41–6.
- Kirby T, Colin Sullivan: inventive pioneer of sleep medicine. *Lancet* 2011;377:485.
- Kushida CA, Littner MR, Hirshkowitz M, et al.; American Academy of Sleep Medicine. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. *Sleep* 2006;29:240–3.
- Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. *Sleep* 2006;29:244–62.
- Cartwright RD, Samelson CF. The effects of a nonsurgical treatment for obstructive sleep apnea. The tongue-retaining device. *JAMA* 1982;13:248:705–9.

- Dort L, Brant R. A randomized, controlled, crossover study of a noncustomized tongue retaining device for sleep disordered breathing. *Sleep Breath* 2008;12:369–73.
- Lazard DS, Blumen M, Lévy P, et al. The tongue-retaining device: efficacy and side effects in obstructive sleep apnea syndrome. *J Clin Sleep Med* 2009;5:431–8.
- Randerath WJ, Verbraecken J, Andreas S, et al.; European Respiratory Society task force on non-CPAP therapies in sleep apnoea. Non-CPAP therapies in obstructive sleep apnoea. *Eur Respir J* 2011;37:1000–28.
- Deane SA, Cistulli PA, Ng AT, Zeng B, Petocz P, Darendeliler MA. Comparison of mandibular advancement splint and tongue stabilizing device in obstructive sleep apnea: a randomized controlled trial. *Sleep* 2009;32:648–53.
- Sutherland K, Deane SA, Chan AS, et al. Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea. *Sleep* 2011;34:469–77.
- Tsuiki S, Shiga T, Maeda K, Matsuzaki-Stromberger R, Inoue Y. A dentist's role: prevention of snoring at temporary refuges for victims of the East Japan earthquake and the Fukushima Daiichi Nuclear Power Plant accident on March 11, 2011. *Sleep Breath* 2012;16:587–9.
- Tsuiki S, Kobayashi M, Namba K, et al. Optimal positive airway pressure predicts oral appliance treatment response to sleep apnoea. *Eur Respir J* 2010;35:1098–105.
- Fukuda T, Tsuiki S, Kobayashi M, Nakayama H, Inoue Y. Selection of response criteria affects the success rate of oral appliance treatment for obstructive sleep apnea. *Sleep Med* 2014;15:367–70.
- Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–89.
- Takegami M, Suzukamo Y, Wakita T, et al. Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on Item Response Theory. *Sleep Med* 2009;10:556–65.
- Isono S, Remmers JE, Tanaka A, Sho Y, Sato J, Nishino T. Anatomy of pharynx in patients with obstructive sleep apnea and in normal subjects. *J Appl Physiol* 1997;82:1319–26.
- Isono S, Tanaka A, Tagaito Y, Sho Y, Nishino T. Pharyngeal patency in response to advancement of the mandible in obese anesthetized persons. *Anesthesiology* 1997;87:1055–62.
- Dort L, Remmers JE. A combination appliance for obstructive sleep apnea: the effectiveness of mandibular advancement and tongue retention. *J Clin Sleep Med* 2012;8:265–9.
- Tsuiki S, Isono S, Minamino O, et al. Tongue position controller as an alternative treatment for obstructive sleep apnea. *Sleep Breath* 2012;16:957–60.

## ACKNOWLEDGMENTS

The present study was supported in part by a Grant-in-Aid for Scientific Research (grant number 25515010, 15H05301) from the Japan Society for the Promotion of Science. The authors greatly thank Mr. Kazuyoshi Namba and Ms. Yuka Suzuki for their data analyses and telephone follow-up. We also thank Dr. Keiko Maeda for her sampling of patients.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication March, 2015

Submitted in final revised form January, 2016

Accepted for publication February, 2016

Address correspondence to: Satoru Tsuiki, DDS, PhD, Division of Dental Sleep Medicine, Japan Somnology Center, Institute of Neuropsychiatry, 1-24-10, Yoyogi, Shibuya-ku, Tokyo, Japan 151-0053; Tel: +81-3-3374-9112; Fax: +81-3374-9125; Email: tsuiki@somnology.com

## DISCLOSURE STATEMENT

This was not an industry supported study. This work was performed at the Institute of Neuropsychiatry and supported in part by a Grant-in-Aid for Scientific Research [grant number 25515010,15H05301] from the Japan Society for the Promotion of Science. The authors have indicated no financial conflicts of interest.



# Health-Related Quality of Life Assessment Tools and Sleep-Disordered Breathing

Rose D. Sheats, DMD, MPH

Orofacial Pain Group, University of North Carolina School of Dentistry, Chapel Hill, NC

Patients, providers, and third-party payers all have a stake in the outcomes of management of medical conditions. As part of the development of the 2015 update of clinical practice guidelines for the treatment of obstructive sleep apnea and snoring with oral appliance therapy (see reference 1), studies were reviewed that included assessments of quality of life outcomes. Patient perception of health-related quality of life has been recognized as important an outcome as the provider's clinical assessment of treatment effectiveness. Tools have been developed to measure relevant domains that contribute to health-related quality of life. These tools may be generic or disease-specific. It is essential to note that assessments of sleep are not equivalent to assessments of health-related quality of life. This review offers for clinicians an introduction to examples of generic and obstructive sleep apnea-specific health-related quality of life instruments and also serves to distinguish such tools from those used to assess sleep.

**KEYWORDS:** health-related quality of life, sleep-disordered breathing, adult quality of life tools, pediatric quality of life tools, treatment outcomes

**CITATION:** Sheats RD. Health-related quality of life assessment tools and sleep-disordered breathing. *Journal of Dental Sleep Medicine* 2016;3(2):49–55.

## INTRODUCTION

In 2015 the American Academy of Sleep Medicine and the American Academy of Dental Sleep Medicine published a joint set of updated clinical practice guidelines for the use of oral appliance therapy (OAT) to treat obstructive sleep apnea and snoring.<sup>1</sup> These guidelines were developed using a set of 11 PICO (patient, population or problem, intervention, comparison, and outcomes) questions that had arisen from previous guidelines and reviews. It is noteworthy that 4 of these 11 PICO questions (#1, 4, 5, & 10) included assessment of the impact of oral appliance therapy on quality of life measures. The final recommendations were based on extensive review of the best literature available and meta-analysis of the evidence. The evidence included outcomes from quality of life studies, signifying that quality of life assessments are considered important in judging therapeutic benefit from OAT.

Dentists who provide oral appliance therapy are familiar with the popular Epworth Sleepiness Scale<sup>2</sup> and polysomnography but may confuse these tools with those that measure health-related quality of life. The distinction between them is important. Release of the new practice guidelines presents an opportunity for timely review of the process of formally measuring quality of life and health-related quality of life (HRQoL) and for distinguishing them from measurement of sleep quality and parameters.

Quality of life is composed of many standards including wealth, environment, happiness, social and community interactions, and physical and mental health. Many instruments or tools have been developed to measure these various dimensions that contribute to an individual's quality of life. Health-related quality of life (HRQoL) instruments measure how a disease, disability, or disorder affects one's life over time.<sup>3</sup> They are also

used to examine the impact of treatment on specific conditions. Physical, mental, and social health comprise important aspects of HRQoL.

Health-related quality of life tools have been developed and validated for use in both clinical and research settings. The best instruments have been rigorously studied to confirm good psychometric parameters such as validity, reliability, and internal consistency, all essential features of well-designed survey instruments.<sup>4</sup> These instruments or tools measure multiple "domains" that refer to categories of health dimensions that compose health-related quality of life. Questions or statements, referred to as "items," are grouped to assess each health dimension, and responses to each group of items are summarized to provide a score for that health dimension.

Responses to questions or statements are usually recorded as yes/no or scored on a Likert scale. A Likert scale is composed of ordered responses that indicate a progression such as worsening (or improvement) of symptoms. Likert scales typically have 3 to 7 options in HRQoL instruments. For example, a 4-point Likert scale measuring ability to perform a specific activity might have the following ordered categories:

1. no difficulty
2. a little difficulty
3. moderate difficulty
4. extreme difficulty.

A 7-point Likert scale assessing the frequency of occurrence of symptoms might look like this:

1. all the time
2. a large amount of the time
3. a moderate to large amount of the time
4. a moderate amount of the time
5. a small to moderate amount of time

6. a small amount of time
7. not at all.

Likert scales can be ordered in either direction. To correctly interpret the results, it is important to know whether high scores or low scores are more desirable for a particular instrument.

Health-related quality of life instruments are either generic or disease or condition-specific. Generic health-related quality of life instruments refer to those questionnaires or tools that can be used across populations and facilitate cross-disease comparisons.<sup>5</sup> Because of their general nature, however, they are not sensitive enough to measure treatment outcomes for specific diseases. Many do not include a sleep domain.

Disease-specific health-related quality of life tools focus on particular features of a specific disease or condition and have been validated to examine the impact of specific diseases and their management on patients' lives. They provide consistent and reliable assessments of impaired HRQoL and are sensitive enough to measure changes that occur as a result of treatment over time. Instruments have been developed for both adult and pediatric assessments.

The purpose of this review is to introduce clinicians to examples of generic as well as obstructive sleep apnea-specific health-related quality of life instruments. These examples were drawn from published studies of sleep-disordered breathing research and are not intended to be all-inclusive of the breadth of such instruments that have been developed. Readers seeking to compare psychometric properties of these instruments are encouraged to review source articles or one of several excellent review articles.<sup>4-8</sup>

When comparing the merits of the following instruments, consideration should be given to the length of the instrument, the administration (interview vs self-administration), the complexity of scoring, and the ease of comparing scores over time.

## GENERIC HEALTH-RELATED QUALITY OF LIFE INSTRUMENTS

### Sickness Impact Profile (SIP)

The Sickness Impact Profile (SIP) was among the earliest and most comprehensive of generic HRQoL instruments.<sup>9</sup> It can be completed either by the patient or by an interviewer. At 136 items, it provides individual scores in each of 12 categories that it assesses: ambulation, mobility, body care and movement, communication, alertness behavior, emotional behavior, social interaction, sleep and rest, eating, work, home management, and recreation and pastimes. Response choices are binary ("Yes/No"). Individual category scores are calculated by a standardized weighting method of item responses. Summary scores for 2 domains, physical and psychosocial, are derived from the categories. A total score is also calculated and is reported as a percentage. Higher scores are associated with poorer level of health.

The SIP has been used to validate subsequent HRQoL instrument development, but its length and complexity of scoring render it impractical for use in clinical practice.

### The Nottingham Health Profile (NHP)

Another early instrument, the Nottingham Health Profile (NHP) was developed in Nottingham, England to include both patient perception of health as well as clinical assessment.<sup>10</sup> It places equal or greater emphasis on the patient's impression of the impact of disease or its treatment on health-related quality of life. The NHP measures 6 health domains via 38 self-administered yes/no questions: energy level, pain, emotional reactions, sleep, social isolation, and physical abilities. Its reliability and validity have been extensively demonstrated in a number of settings. Scores are weighted according to an algorithm and range from 0 to 100 for each domain, with higher scores representing greater perceived problems in that domain.

Although patients may be amenable to completing a 38-item questionnaire, scoring of the instrument requires an algorithm that would likely be burdensome in a clinical practice.

### The Medical Outcomes Study Short Form-36 (SF-36)

The Medical Outcomes Study Short Form-36 (SF-36) was developed as part of a multi-year, multi-site study to investigate variations in patient medical outcomes.<sup>11</sup> This 36-item survey can be either interviewer- or self-administered and measures 8 health domains: physical functioning, role limitations due to physical problems, bodily pain, social functioning, mental health, role limitations due to emotional problems, vitality, and perception of general health. A score for each health domain is derived. A final question inquires about perception of change in health from the previous year. Most items are scored on a 3–6 point Likert-type scale. High scores are indicative of favorable responses in each scale.

Because domains vary in the number of items from 2–10, interpretation of domain scores is not easily intuited and in clinical practice would be facilitated by the use of a table.<sup>11</sup> The SF-36 is considered the gold standard of HRQoL instruments<sup>12</sup> and is widely used in the validation of new HRQoL tools including each of the adult OSA-specific HRQoL instruments described below.

### The Medical Outcomes Study Short Form-12 (SF-12)

The Medical Outcomes Study Short Form-12 was constructed by using regression methods to identify 12 items from the SF-36 to derive scores for a Physical Component Summary and Mental Component Summary of health-related quality of life.<sup>13</sup> While loss of precision in assessing health occurs by reducing the number of items, the SF-12 can be administered in less than 2 minutes and is useful for population studies where cost and time may otherwise be prohibitive in the use of the SF-36. For assessments of an individual's health, however, the 8 scales of the SF-36 are more reliable and offer a more precise representation of specific health domains. Thus is it more sensitive to changes that may occur over time or as the consequence of intervention in individual patients.

### Behavioral Risk Factor Surveillance System (BRFSS) Health-Related Quality of Life Module

The Centers for Disease Control (CDC) judged that the length of both the SF-36 and SF-12 rendered them impractical for large scale implementation. Thus the CDC developed a module



**Table 1**—Generic health related quality of life instruments.

Instrument Name	Health Domains Addressed	Number Items	Scoring	Scoring Interpretation
Sickness Impact Profile (SIP) <sup>9</sup>	2 overall domains (Physical and Psychosocial) 12 categories: Ambulation, mobility, body care and movement, communication, alertness behavior, emotional behavior, social interaction, sleep and rest, eating, work, home management, and recreation and pastimes.	136	Yes/no format	Increasing numbers of “yes” responses indicate greater impact on health
Nottingham Health Profile (NHP) <sup>10</sup>	6 domains: Physical mobility, pain, social isolation, emotional reactions, energy, sleep	38	Yes/no format	Responses are weighted with scores ranging from 0–100 for each domain. Higher scores indicate greater health problem
Medical Outcomes Study Short-Form 36 (SF-36) <sup>11</sup>	8 domains: Physical functioning, role limitations due to physical problems, bodily pain, social functioning, mental health, role limitations due to emotional problems, vitality, and perception of general health	36	3–6 point Likert scales	Higher scores indicate better quality of life
Medical Outcomes Study Short-Form 12 (SF-12) <sup>13</sup>	2 overall domains: Health Component Summary (HCS), Mental Component Summary (MCS)	12	Yes/no or 3–6 point Likert scales	Complex scoring requiring purchase of scoring algorithm from developer
Behavioral Risk Factor Surveillance System (BRFSS) <sup>14</sup>	BRFSS HrQoL-4: Self-perceived health, recent physical health, recent mental health, recent activity limitation BRFSS HrQoL-14: Above 4 items plus 10 additional items that assess activity limitation and persistent short-term and persistent physical and mental health problems	4 or 14	4 or 5 ordered categories indicating progressively worse health status	Qualitative and quantitative assessments; quantitative assessments refer to # days of self-rated poor health
Child Health Questionnaire (CHQ-PF50) <sup>15</sup>	14 domains: Physical functioning, Role/social limitations – physical, General health perceptions, Bodily pain/discomfort, Family activities, Role/social limitations – emotional/behavioral, (considered 2 domains), Parent impact – time, Parent impact – emotion, Self-esteem, Mental health, Behavior, Family cohesion, Change in health	50	4–6 Likert-type responses	Subscale scores range from 0–100. Higher scores associated with better health state. Scoring and interpretation manual required

on HRQoL composed of 4 questions to supplement the State-based Behavioral Risk Factor Surveillance System (BRFSS). The module enabled local and State agencies to collect data on health related quality of life.<sup>14</sup> The 4 questions on HRQoL were developed after the CDC convened several meetings, beginning in 1991, with experts in quality of life assessments, surveillance methodology, and public policy.<sup>14</sup> The 4 questions address self-perceived general health, recent (past 30 days) physical health, recent mental health, and activity limitation. Responses are recorded as number of days in the past 30 that the respondent experienced problems in each item (except for self-perceived general health which is recorded on a 5-point Likert scale). The greater the number, the worse the perceived health.

For those States that wish to collect more detailed HRQoL information, the CDC designed the HRQoL-14 as a supplemental optional 10-question module. These additional questions were validated using the SF-36 and assess Standard Activity Limitation and Healthy Days Symptoms to provide information on the burden of diseases and benefits of interventions.<sup>3</sup>

While it is tempting to utilize the CDC’s brief modules to assess HRQoL, the BRFSS health-related quality of life modules were specifically designed for population assessments, and, as such, are much too broad to be useful in evaluating individual patients. Nevertheless, the 2 modules are models with respect to desirable features of a simple, brief, and meaningful HRQoL survey.

### Child Health Questionnaire - Parent Form 50 (CHQ-PF50)

This 50-item questionnaire is completed by the parent and was designed to measure HRQoL in children > 5 years of age.<sup>15</sup> It assesses 14 physical and psychosocial domains and has been used to assess HRQoL in children with sleep disordered breathing.<sup>16</sup> Item responses consist of 4 to 6 Likert-type choices. Subscale scores range from 0–100 with higher scores indicating better health state. This instrument does not lend itself to use in clinical practice as a scoring and interpretation manual are required.<sup>15</sup>

**Table 1** provides a comparison of these generic health-related quality of life instruments.

## DISEASE-SPECIFIC HEALTH-RELATED QUALITY OF LIFE INSTRUMENTS

Surveys developed specifically to evaluate the impact of obstructive sleep apnea on HRQoL include questionnaires that have been designed separately for adult and pediatric patients. Such instruments are specific for features of obstructive sleep apnea and are thus more sensitive to changes in disease condition that occur over time. They are useful for measuring the effect of treatment and therefore are more appropriate than generic health-related quality of life tools to document therapeutic

outcomes on HRQoL of individual patients. Obstructive sleep apnea-specific HRQoL tools that have been identified by review of the literature are described below. They are grouped by suitability for either adult or pediatric patients.

## Adult Disease-Specific Health-Related Quality of Life Instruments

### *Functional Outcomes of Sleep Quality (FOSQ)*

This widely-used instrument was the first disease-specific HRQoL survey that met rigorous psychometric criteria which confirmed its utility in clinical and research settings.<sup>17</sup> First described in 1997, the FOSQ measures the impact of excessive sleepiness on functional activities of daily living. This 30-item self-administered survey measures 5 domains of health that are affected by quality of sleep and has been demonstrated to have excellent validity. The health domains assess general productivity, vigilance, social outcome, activity level, and intimacy/sexual relationships. Scores from the 5 components are used to calculate a global score.

Scoring algorithms are included with the survey and describe how to weight subscale scores and to use these weighted scores to arrive at a total score, which can range from 5 to 20. The lower the score, the greater the impact of excessive sleepiness.

### *FOSQ-10*

A shorter version of the 30-item FOSQ was developed to facilitate implementation into clinical practices.<sup>18</sup> This 10-item self-administered version measures the same 5 domains as the longer version and is capable of measuring meaningful changes in disease impact. The FOSQ-10 has been demonstrated to have similar psychometric properties as the longer version and is thus suitable for assessing the HRQoL impairment resulting from excessive sleepiness.

As in the original FOSQ instrument, mean weighted subscale scores are calculated to derive a total score according to the scoring algorithm. While not an arithmetically complex algorithm, effort must be expended to compute the total score.

### *Calgary Sleep Apnea Quality of Life Index*

The Calgary Sleep Apnea Quality of Life Index (SAQLI) is an interview-administered instrument that assesses patients' health-related quality of life over the previous 4 weeks.<sup>19</sup> This 45-item survey assesses 4 domains: daily functioning, social interactions, emotional functioning, and symptoms. Furthermore, patients also rank the impact of each item on their functioning. The SAQLI is unique in that a fifth domain, treatment-related symptoms, can be assessed after treatment has been initiated, thus rendering this instrument especially attractive to clinicians seeking to evaluate not only patient-perceived treatment effectiveness and but also side effects of treatment.

Patients rate each item on a 7-point Likert scale. Responses are weighted according to the importance of the problem that the patient assigns to each item. The somewhat elaborate scoring algorithm, however, may pose a challenge to efficient implementation in clinical practice.

### *Obstructive Sleep Apnea Patient-Oriented Severity Index (OSAPOS)*

The Obstructive Sleep Apnea Patient-Oriented Severity Index (OSAPOS) was developed to measure, from the patient's perspective, pre-treatment and post-treatment physical, functional, and emotional aspects of obstructive sleep apnea (OSA) on health-related quality of life.<sup>20</sup> This self-administered 32-item survey is organized into 5 subscales: sleep, awake, medical, emotional and personal, and occupational impact. Each item is scored twice: once to indicate the magnitude of the problem and a second time to record the patient's judgment of how significantly the problem affects the patient's HRQoL. The product of these 2 scores generates a symptom-impact score for each item. The symptom-impact score for each item ranges from 0 to 20 with a maximum total score on the entire instrument ranging from 0 to 640. Higher scores indicate worse HRQoL.

In 2000 a modified version of this instrument was described and renamed the Symptoms of Nocturnal Obstruction and Related Events-25 (SNORE-25).<sup>21</sup> Seven items were removed, and the scoring was simplified to eliminate the need for patients to provide a second scoring of importance of the problem. Instead, after recording the magnitude of each problem, patients may list up to 5 of the most significant items that they hope will improve with treatment.

### *Quebec Sleep Questionnaire*

The Quebec Sleep Questionnaire (QSQ) utilizes 32 items to measure 5 HRQoL domains: daytime sleepiness, diurnal symptoms, nocturnal symptoms, emotions, and social interactions.<sup>22</sup> This self-administered instrument was developed specifically to capture changes that occur in quality of life as a consequence of treatment for OSA and has been demonstrated to be sufficiently sensitive to treatment impact. The authors acknowledge the similarity of the QSQ and the SAQLI in that both instruments were designed with the specific intent of evaluating the impact of treatment on sleep disordered breathing. However, the selection of items that compose the 2 instruments was determined by different methods. The SAQLI items were identified by the "factor analysis method" (a statistical method) while the QSQ items were chosen based on the "clinical impact method" whereby clinical judgment is used to select the items that compose the different domains. Both methods are deemed valid, and while the domains significantly overlap, the specific items that are assessed differ.

Item scores range from 1 to 7. Mean scores for each domain are calculated, and a total score is derived by calculating the mean of all items. Higher scores are associated with better HRQoL.

**Table 2** summarizes these adult disease specific health-related quality of life instruments.

## Pediatric Disease-Specific Health-Related Quality Of Life Instruments

### *Obstructive Sleep Apnea-18 (OSA-18)*

The OSA-18 is a caregiver-administered health-related quality of life assessment tool for pediatric patients with OSA.<sup>23</sup> Its 18

**Table 2**—Adult OSA-specific health related quality of life instruments.

Instrument Name	Health Domains Addressed	Number Items, Scoring	Scoring	Scoring Interpretation
Functional Outcomes of Sleep Quality (FOSQ) <sup>17</sup>	5 domains: General productivity, vigilance, social outcome, activity level, and intimacy/sexual relationships	30	5-point Likert scale	Lower scores indicate greater impairment
FOSQ-10 <sup>18</sup>	5 domains: General productivity, vigilance, social outcome, activity level, and intimacy/sexual relationships	10	5-point Likert scale	Lower scores indicate greater impairment
Calgary Sleep Apnea Quality of Life Index (SAQLI) <sup>19</sup>	4 domains: Daily functioning, social interactions, emotional functioning, and symptoms; optional 5 <sup>th</sup> domain assessing side effects of treatment	45	7-point Likert scale	Higher scores indicate better quality of life
Obstructive Sleep Apnea Patient-Oriented Severity Index (OSAPOS) <sup>20</sup>	5 domains: Sleep disturbance, physical symptoms, emotional symptoms, daytime functioning, and caregiver concerns	32	Each item scored by two scales: “Magnitude of problem scale” 5-point Likert scale; “Importance scale” 4-point Likert scale; Impact score calculated = Magnitude × Importance	Higher score indicates worse quality of life
Quebec Sleep Questionnaire <sup>22</sup>	5 domains: Daytime sleepiness, diurnal symptoms, nocturnal symptoms, emotions, and social interactions	32	7-point Likert scale	Higher scores indicate better quality of life

items assess 5 domains: sleep disturbance, physical symptoms, emotional symptoms, daytime functioning, and caregiver concerns. Its validity and reliability have been demonstrated for pediatric OSA patients between 6 months and 12 years of age. Higher scores are associated with larger impact of OSA on HRQoL. Scores < 60 suggest a small impact on HRQoL.

#### *Cohen’s Pediatric OSA Surgery Quality of Life Questionnaire*

Cohen’s Pediatric OSA Surgery Quality of Life Questionnaire is a survey of 76 items completed by parents of children 2 to 7 years old who underwent either tracheostomy or sleep apnea surgery.<sup>24</sup> This instrument is unique in its inclusion of a cost domain. Designed to capture pre- and post-treatment impact on HRQoL, it assesses 3 domains: physical symptoms, psychosocial function, and costs which are measured both in numbers of medical visits as well as by out-of-pocket expenses. Items are scored on a 5-point Likert scale with lower rankings being associated with better outcomes.

**Table 3** summarizes these pediatric disease specific health-related quality of life instruments.

## **SLEEP ASSESSMENTS DO NOT MEASURE HEALTH-RELATED QUALITY OF LIFE**

Quality of sleep is an important contributor to daytime functioning and long-term health, but the sleep domain by itself does not encompass the many dimensions that comprise HRQoL. Tools to evaluate sleep physiology, sleepiness, and sleep quality are briefly described in this review in an effort to clarify the distinction between instruments that assess sleep and those that measure HRQoL.

Evaluation of sleepiness and sleep parameters provides useful information on the effectiveness of treatment in

improving the sleep domain and thus sleep-associated outcomes. Dentists will recognize these tools as they are routinely included in medical referrals and patient follow-up exams. Common instruments to evaluate sleep physiology and sleepiness include polysomnography<sup>25</sup> and the Epworth Sleepiness Scale.<sup>2</sup> The Pittsburgh Sleep Quality Index<sup>26</sup> is also discussed to demonstrate that sleep quality includes more domains than just sleepiness.

### **Polysomnography**

Polysomnography (PSG) provides information on sleep physiology (e.g. sleep stages, sleep architecture, sleep efficiency, oxygen levels) and is limited to documenting, in great detail, objective parameters of sleep,<sup>25</sup> one domain among many that compose health-related quality of life. PSG parameters such as the apnea-hypopnea index, oxygen saturation levels, sleep efficiency, and sleep stages lend themselves to easy comparisons over time as long as one recognizes the limitation of night-to-night variability that occurs in subjects. PSG is useful for documenting changes in objective sleep parameters secondary to treatment intervention but does not measure changes in daytime functioning or health-related quality of life.

### **Epworth Sleepiness Scale (ESS)**

The Epworth Sleepiness Scale (ESS) is a widely used tool to measure excessive daytime sleepiness (EDS) because of its simplicity of use.<sup>2</sup> This 8-question survey is self-administered, poses little burden to the practice, and provides a single score that can be compared over multiple visits. Scores range from 0 to 24; scores > 10 indicate the presence of EDS. While this questionnaire assesses the impact of sleepiness on daytime functioning, it is not specific for sleep disordered breathing. Other causes of EDS such as chronic or acute pain and emotional distress may better explain EDS in some patients.

**Table 3**—Pediatric OSA-specific health related quality of life instruments.

Instrument Name	Health Domains Addressed	Number Items	Scoring	Scoring Interpretation
Obstructive Sleep Apnea-18 (OSA-18) <sup>23</sup>	5 domains: Sleep disturbance, physical symptoms, emotional symptoms, daytime functioning, and caregiver concerns	18	7-point frequency scale rated by caregiver	Higher scores associated with greater impact on HRQoL; < 60 suggests small impact on HRQoL
Cohen's Pediatric OSA Surgery Quality of Life Questionnaire <sup>24</sup>	3 domains: Physical symptoms, psychosocial function, and costs	76	Most scored on 5-point Likert scale	Varies with each item: higher scores favorable for some items but unfavorable for others

**Table 4**—Sleep assessments.

Instrument Name	Domains	Number Items	Scoring	Scoring Interpretation
Polysomnograms <sup>25</sup>	Not applicable	Multiple channels	Hypnogram tracing	Objective assessment, no subjective assessment
Epworth Sleepiness Scale <sup>2</sup>	Daytime sleepiness	8	4 point Likert scale	≤ 10 normal; > 10 suggests excessive daytime sleepiness
Pittsburgh Sleep Quality Index <sup>26</sup>	7 domains: Subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction	19	4-point Likert scale (0–3)	Global score = sum of domain scores Global score ranges from 0–21; higher scores indicate poorer sleep quality

### Pittsburgh Sleep Quality Index (PSQI)

The Pittsburgh Sleep Quality Index (PSQI) is a tool that was developed to evaluate the quality of sleep over a one-month period in psychiatric patients.<sup>26</sup> This survey was validated using both healthy patients (“good sleepers”) and depressed patients (“poor sleepers”) and is composed of 19 self-rated items that evaluate both quantitative and qualitative information. Seven domains are assessed: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleep medication, and daytime dysfunction. Item scores range from 0 to 3 per item, and a summary component score of 0–3 is determined according to the scoring algorithm for each component. The sum of the 7 component scores generates a single global score which can be used for easy longitudinal comparisons of changes in a patient’s sleep quality. Global scores range from 0–21. Higher scores indicate poorer sleep quality.

**Table 4** provides a summary of these sleep assessment tools. While evaluation of sleep provides useful information on a critical component of health-related quality of life, by themselves such tools are not suitable as global assessments of health-related quality of life.

## DISCUSSION

Patients, providers, and third-party payers all have a stake in the outcomes of management of medical conditions, especially with the advent of the Affordable Care Act. The Centers for Medicaid and Medicare Services (CMS) has developed a set of quality metrics to improve patient care and outcomes of many diseases.<sup>27</sup> Quality metrics are reported to CMS via the Physician Quality Reporting System (PQRS), a program that was first implemented in 2006 as a temporary measure under the

Physician Quality Reporting Initiative. In 2010 the Affordable Care Act made the program permanent, and the name was changed to the Physician Quality Reporting System. Although the reporting requirement is considered voluntary, beginning in 2015, Medicare reimbursement rates are being “negatively adjusted” for providers of Part B covered services who do not satisfactorily report quality metrics to CMS.<sup>28</sup>

The American Academy of Sleep Medicine (AASM) spearheaded the effort to develop for CMS appropriate outcome measures for the sleep apnea quality metrics.<sup>29</sup> The AASM acknowledged that although health-related quality of life measurements are not typically collected during routine clinical evaluations, such evaluations provide one of the best assessments of effective patient treatment. The AASM report did not mandate use of a specific HRQoL tool and instead deferred to clinician choice in order to minimize the burden to the practice.

At present, no PQRS measures have been established for oral appliance therapy (OAT), thus dentists who provide this treatment to Medicare recipients are not currently required to report data to CMS on quality measures for OAT. However, the changing healthcare climate may lead to incorporation of such outcomes into future practice guidelines or reimbursement policies. At that time, it would behoove dental sleep medicine practitioners to be prepared to identify what instruments are available and to understand features of HRQoL tools that would expedite compliance with such guidelines.

## SUMMARY

Of the currently available obstructive sleep apnea specific health-related quality of life instruments, dentists will likely find that the following are most user-friendly: the Functional



Outcomes of Sleep Quality-10 (FOSQ-10), the Calgary Sleep Apnea Quality of Life Index (SAQLI), or the Quebec Sleep Questionnaire (QSQ). Clinicians should note, however, that scoring for all three tools necessitates calculations which may constitute a barrier to facile implementation in clinical practice.

Measurement of HRQoL outcomes of OAT may be facilitated by development of a brief and clinically useful tool that can be rapidly deployed in a busy dental practice. Desirable features of such an OSA-specific HRQoL instrument with acceptable psychometric parameters include the ability to be self-administered, ease of patient completion, straightforward scoring, and a single overall score for comparison across time.

It is clear from review of these generic and OSA-specific health-related quality of life instruments that common dimensions emerge that are deemed to be important aspects of a favorable health-related quality of life. As health care providers, we should aspire not only to diminishing the unfavorable medical sequelae of sleep disordered breathing but also to enhancing our patients' energy levels and vitality, social and community interactions, work productivity, mental alertness, and overall general well-being.

## REFERENCES

- Ramar K, Dort LC, Katz SG, et al. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. *J Clin Sleep Med* 2015;11:773–827.
- Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep* 1991;14:540–5.
- Centers for Disease Control and Prevention. *Measuring healthy days: Population assessment of health-related quality of life*. Atlanta, GA: Centers for Disease Control and Prevention, 2000.
- Guyatt GH, Naylor CD, Juniper E, Heyland DK, Jaeschke R, Cook DJ. Users' guides to the medical literature. XII. How to use articles about health-related quality of life. Evidence-Based Medicine Working Group. *JAMA* 1997;277:1232–7.
- Reimer MA, Flemons WW. Quality of life in sleep disorders. *Sleep Med Rev* 2003;7:335–49.
- Coons SJ, Rao S, Keininger DL, Hays RD. A comparative review of generic quality-of-life instruments. *Pharmacoeconomics* 2000;17:13–35.
- Moyer CA, Sonnad SS, Garetz SL, Helman JL, Chervin RD. Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med* 2001;2:477–91.
- Hullmann SE, Ryan JL, Ramsey RR, Chaney JM, Mullins LL. Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML). *Arthritis Care Res* 2011;63:S420–S430.
- Bergner M, Bobbitt RA, Carter WB, Gilson BS. The Sickness Impact Profile: development and final revision of a health status measure. *Med Care* 1981;19:787–805.
- Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. *J R Coll Gen Pract* 1985;35:185–8.
- Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
- Weaver TE. Outcome measurement in sleep medicine practice and research. Part 1: assessment of symptoms, subjective and objective daytime sleepiness, health-related quality of life and functional status. *Sleep Med Rev* 2001;5:103–28.

- Ware JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care* 1996;34:220–33.
- Hennessy CH, Moriarty DG, Zack MM, Scherr PA, Brackbill R. Measuring health-related quality of life for public health surveillance. *Public Health Rep* 1994;109:665–72.
- HealthActCHQ. CHQ: Child Health Questionnaire (n.d.). Retrieved from <http://www.healthact.com/chq.php>.
- Rosen CL, Palermo TM, Larkin EK, Redline S. Health-related quality of life and sleep-disordered breathing in children. *Sleep* 2002;25:657–66.
- Weaver TE, Laizner AM, Evans LK, et al. An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep* 1997;20:835–43.
- Chasens ER, Ratcliffe SJ, Weaver TE. Development of the FOSQ-10: a short version of the Functional Outcomes of Sleep Questionnaire. *Sleep* 2009;32:915–9.
- Flemons WW, Reimer MA. Development of a disease-specific health-related quality of life questionnaire for sleep apnea. *Am J Respir Crit Care Med* 1998;158:494–503.
- Piccirillo JF, Gates GA, White DL, Schectman KB. Obstructive sleep apnea treatment outcomes pilot study. *Otolaryngol Head Neck Surg* 1998;118:833–44.
- Piccirillo JF. Outcomes research and obstructive sleep apnea. *Laryngoscope* 2000;110:16–20.
- Lacasse Y, Bureau MP, Series F. A new standardised and self-administered quality of life questionnaire specific to obstructive sleep apnoea. *Thorax* 2004;59:494–9.
- Franco RA Jr., Rosenfeld RM, Rao M. First place--resident clinical science award 1999. Quality of life for children with obstructive sleep apnea. *Otolaryngol Head Neck Surg* 2000;123:9–16.
- Cohen SR, Suzman K, Simms C, Burstein FD, Riski J, Montgomery G. Sleep apnea surgery versus tracheostomy in children: an exploratory study of the comparative effects on quality of life. *Plast Reconstr Surg* 1998;102:1855–64.
- Berry RB, Brooks R, Gamaldo CE, Harding SM, Lloyd RM, Marcus CL, Vaughn BV; for the American Academy of Sleep Medicine. AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, Version 2.2. [www.aasmnet.org](http://www.aasmnet.org). Darien, IL: American Academy of Sleep Medicine, 2015.
- Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
- Centers for Medicare and Medicaid Services. Physician Quality Reporting System: Measures Codes. July 10, 2015. Retrieved from: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/MeasuresCodes.html>
- Centers for Medicare and Medicaid Services. Physician Quality Reporting System. (n.d.) Retrieved from: <http://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-Instruments/PQRS/Payment-Adjustment-Information.html>
- Aurora RN, Collop NA, Jacobowitz O, Thomas SM, Quan SF, Aronsky AJ. Quality measures for the care of adult patients with obstructive sleep apnea. *J Clin Sleep Med* 2015;11:357–83.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication August, 2015

Submitted in final revised form February, 2016

Accepted for publication February, 2016

Address correspondence to: Rose D. Sheats, University of North Carolina, School of Dentistry, CB 7450, Chapel Hill, NC 27599; Email: [Rose\\_Sheats@unc.edu](mailto:Rose_Sheats@unc.edu)

## DISCLOSURE STATEMENT

This was not an industry supported study. Dr. Sheats has indicated no financial conflicts of interest.



# Skeletal Malocclusion and Genetic Expression: An Evidence-Based Review

Clarice Nishio, DDS, MSc, PhD; Nelly Huynh, PhD

Faculty of Dentistry, University of Montreal, Quebec, Canada

Altered dentofacial morphology is an important risk factor of obstructive sleep apnea by compromising the upper airway volume. Maxillary and/or mandibular retrognathia, narrow maxilla, and long face are the most common craniofacial risk factors of sleep-disordered breathing. The etiology of dentofacial variation and malocclusion is multifactorial, which includes the influence of genetic and environmental factors acting on the units of the craniofacial complex. There is very little evidence on the reverse relationship, where changes in malocclusion could affect gene expression. The advances in human genetics and molecular biology have contributed to the identification of relevant genetic markers associated with certain skeletal malocclusions and/or dental malformations. Since some studies have observed differences between siblings, between parents/children, and between monozygotic twin pairs, this evidence suggests a significant influence of environmental factors in the development of dentofacial structures. However, the skeletal craniofacial complex has been systematically documented to be more influenced by genetic factors than the dental malocclusion. The greater the genetic component, the lower the rate of success on the outcome of orthodontic treatment. The real therapy should be an eventual modification of the gene responsible for the malocclusion; however, this is yet a theoretical proposition. The identification of major genes and determination of their biochemical action to a particular jaw discrepancy is the first approach necessary for the search of a solution. Early detection of the consequences of abnormal craniofacial development and assessment of orthodontic practices may validate the treatments used and change the natural history of pediatric obstructive sleep apnea, thereby possibly preventing or delaying the development of sleep apnea in adulthood.

**KEYWORDS:** genetics, genes, mutations, skeletal malocclusion, dental malocclusion

**CITATION:** Nishio C, Huynh N. Skeletal malocclusion and genetic expression: an evidence-based review. *Journal of Dental Sleep Medicine* 2016;3(2):57–63.

## INTRODUCTION

Altered dentofacial morphology represents a major risk factor for obstructive sleep apnea by reducing the upper airway volume. Malocclusions, such as maxillary and/or mandibular retrognathia, narrow maxilla, and long face are the most common craniofacial risk factors of sleep-disordered breathing.<sup>1,2</sup> Malocclusion is the development of a complex trait condition and relationship between both dental arches, in which occlusion has deviated from what is defined as ideal or normal occlusion. Malocclusion should not be considered as abnormal or pathological, instead as a variation of occlusion in a continuous multifactorial trait.<sup>3–7</sup> The etiology of dentofacial variation and malocclusion is multifactorial, which includes the influence of genetic and environmental factors acting on the units of the craniofacial complex, such as bone, teeth, and muscles.<sup>5,6,8–13</sup> However, there is very little evidence on the reverse relationship, where changes in malocclusion could affect gene expression.

## DENTOFACIAL MORPHOLOGY AND GENETICS

Although new technologies have allowed the development of genetic studies, treatment objectives and therapeutic methods have not yet considered the genetic differences between individual patients.<sup>13</sup> Among the reasons for this lack of progress are the limitations of genetic research on human populations and the different methods and concept of malocclusion used

by researchers.<sup>3</sup> Most studies on malocclusion use the Angle's classification system, which is based simply on the dental occlusion variation of permanent first molars. While routinely used in orthodontic practice, this classification presents various deficiencies because it does not consider other vertical and transversal dental occlusion, does not evaluate the relationship of the maxilla and mandible to the cranial base, and finally, does not consider the variation among individuals.<sup>3,14</sup> However, due to the wide consensus upon Angle's classification among researchers, the present manuscript will use this classification system to describe similar patterns of imbalance between the jaws, but will place the term "skeletal" in front of each type of malocclusion; Class I, Class II, and Class III. Although the prevalence of these skeletal malocclusions varies according to the age, race, and population studied, it has been described to be on average 60% Class I, 35% Class II, and 5% Class III in population of western European descent.<sup>15</sup> In the United States, Class II is present in 15% and Class III in 1% of the population.<sup>16,17</sup> Regarding the two divisions of skeletal Class II, studies in Colombian and Iranian populations have showed that the prevalence of patients Class II, division 1 (14.9% to 24%) is higher than Class II, division 2 (3.4% to 5.9%).<sup>18,19</sup>

The recent advances in human genetics and molecular biology have contributed to the identification of relevant genetic markers associated with certain skeletal malocclusions and/or dental malformations. Among many study designs used to understand the role of genetics on malocclusion, there are studies on the skulls of ancient populations,

animal models and investigation within family members and twins.<sup>4,11,12,20–25</sup> Since some of these studies have observed notable differences between siblings, between parents and children, and even between monozygotic twin pairs, this evidence suggests a significant influence of environmental factors in the development of dentofacial structures.<sup>5,6,26,27</sup> However, the skeletal craniofacial complex has been systematically documented to be more influenced by genetic factors than the dental malocclusion.<sup>20</sup> Specific parts of the mandible, such as the lingual symphysis, the lateral surface of the ramus and the frontal curvature of the mandible have been described to be more susceptible to genetic control. On the other side, the antegonial notch of the mandible seems to be more influenced by environmental factors.<sup>20,22</sup> The anterior cranial base, mandibular body length, and total and lower face heights have demonstrated highly hereditary variations.<sup>25,28</sup> More important than to determine the degree of importance of genetics versus environmental factors in the etiology of skeletal malocclusion, is to contemplate the effect of genotype-environment interaction (epigenetic) mechanisms on the multifactorial trait in humans. Although there is not an ideal method to study the genetics of a human trait, studies using complex segregation analysis are the first step to determine if familial aggregation of a given phenotype is due to polygenes, major genes, and/or environment factors.<sup>23</sup>

The objective of this manuscript is to provide a comprehensive review of literature of the evidence for the genetic influence in the skeletal malocclusion. It is worth noting that the genetic determination on dentofacial morphology does not localize only in the bones, but it has also an influence in the neurological, muscular, and neuromuscular spheres, which have an indirect effect on the skeleton. Therefore, this review has also included studies on the genes affecting the muscular pattern of the masticatory complex. Although some dental malformations and syndromes have also been well documented to be associated with moderate to high heritability, respectively, these two subjects will not be exploited in the present review. A systematic literature search was performed electronically in three databases (PubMed, Embase, and Medline) supplemented by a hand search and articles published from 1974 until March 2015. Search terms were combined as follows: genetics, genes, mutations, skeletal malocclusion, dental malocclusion.

### Skeletal Class II, Division 1 Malocclusion

Skeletal Class II malocclusion, either division 1 or 2, is characterized by a mandibular retrusion, a maxillary protrusion, or a combination of both.<sup>20,29</sup> Patients Class II, division 1, can also present anterior upward or downward tipping of the maxilla, steep mandibular plane angle with or without increased lower face height, and a high prevalence of transverse maxillary deficiency. The maxillary incisors have been reported to be normal or proclined, and the mandibular incisors can be in a normal, proclined, or even in a retroinclined position.<sup>15,17</sup>

Although studies have supported the concept of polygenic mode of inheritance for the skeletal Class II malocclusion, the environment has also been described to play an important role on this malocclusion.<sup>3</sup> Adverse parafunctions, such as digital sucking, lip incompetence, protruding tongue, and nasal

airway obstruction have been also associated with the induction of a clockwise rotation of the mandible and an overgrowth of the maxillary alveolar process in these patients.<sup>20,29–31</sup>

A small study of Colombian families with mandibular hypoplasia has suggested a gene candidate of this jaw size discrepancy. The human *NOGGIN* genes are a modulator of the bone morphogenic protein and essential for various late events in mandibular development. This study has shown that all individuals affected with mandibular hypoplasia were homozygous for the rare allele of the polymorphism rs1348322 within the *NOG* gene.<sup>32</sup> Another group of genes that merits attention is the *SNAIL* family of zinc-finger transcription factors. These genes are important in epithelial to mesenchymal transitions and contribute to the formation of the mesoderm and the neural crest.<sup>33</sup> The neural crest-specific deletion of *Snai* on a *Snai2*<sup>-/-</sup> background has been shown to cause craniofacial defects in mice, such as cleft palate and mandibular deficiency, indicating that these *SNAIL* genes may regulate the upper and lower jaw growth.<sup>34</sup> Recently, da Fontoura et al.<sup>35</sup> genotyped individuals with skeletal Class II for 198 single-nucleotide polymorphisms in 71 craniofacial genes and loci. They found that *FGFR2* was associated with increased risk for Class II malocclusion when compared to the control group (Class I), while *EDNI* was correlated with reduced risk.

Methods using the combination of principal component analysis and cluster analysis applied to data from cephalometric radiographs have provided further insight into the characterization of Class II malocclusion phenotypes. Moreno Uribe et al.<sup>17</sup> identified seven principal components of Class II that accounted for 81% of the variation, representing a variation on mandibular rotation, maxillary incisor angulation, and mandibular length. They identified, by cluster analyses, five distinct types of Class II phenotypes.<sup>17</sup> This study, although descriptive, gives an important evidence of the different variation of Class II traits, which indicates a significant participation of the interaction of genotype and environment on the regulation of skeletal Class II malocclusions.

### Skeletal Class II, Division 2 Malocclusion

The skeletal Class II, division 2 malocclusion is characterized by a distinct and consistent clinical phenotype, which includes a combination of retroinclined incisors, deep overbite, high lip line with a lower lip trap, and high activity of the mentalis muscle. These patients often present a counter-clockwise rotation of mandibular development, prominence of the chin, and reduced lower face height.<sup>15,20</sup> All the candidate genes for the mandibular retrognathism and deep-bite traits described in the anterior sections are associated as well with this type of division of Class II.

While some studies have described the mode of inheritance of this type of malocclusion as autosomal dominant with incomplete penetrance and variable expressivity; a polygenic model with expression of a number of genetically determined morphological traits has also been correlated to the Class II, division 2.<sup>20</sup> This malocclusion has also been associated with higher incidence of numerous congenital tooth anomalies, such as missing teeth, peg-shaped laterals, transpositions, supernumerary teeth, and canine impactions, suggesting that



genetic factors related to dental development may also play a role in the maxillomandibular size discrepancies.<sup>36</sup>

### Skeletal Class III Malocclusion

Among all the types of sagittal skeletal discrepancies, the skeletal Class III is the malocclusion the most studied genetically. Class III malocclusion is caused by a deficiency of the maxilla growth, excessive mandibular growth, or a combination of both.<sup>20,23,29</sup> It is characterized by a composite of a dentoskeletal pattern consisting of a forward positioning of the mandibular teeth in relation to the maxillary teeth and a concave profile.<sup>16</sup> The Habsburgs, one of Europe's royal families is an example of Mendelian inheritance of mandibular prognathism, which was observed in several generations of this family, so-called "Habsburg jaw." Although some authors<sup>37</sup> consider that the X chromosome might have some role in mandibular prognathism, some other studies have verified that this trait is not X-linked since both genders are equally affected.<sup>23</sup> It has been observed for many years that mandibular prognathism and probably maxillary deficiency contains not only a genetic component, but also an the influence of environmental factors.<sup>38</sup> The mandibular prognathism has been reported to be a multifactorial and polygenic trait, with a threshold for expression. A study with 2,562 members from 55 families with at least one member affected with the mandibular prognathism described an autosomal dominant mode of transmission with incomplete penetrance and a heritability of 0.316.<sup>23</sup> Taken together, these findings suggest a dominant major gene associated with the expression of mandibular prognathism and an autosomal Mendelian mode of inheritance with the influence of other genes and environmental factors.<sup>23,39</sup> However, another study using segregation analysis of Korean families affected with the mandibular prognathism suggested that the inherited susceptibility to this malocclusion is caused by a combination of minor effects from a variety of different genes and/or environmental influence, rather than an autosomal Mendelian transmission of major genes.<sup>40</sup>

Interestingly, the study of Stahl et al.<sup>41</sup> observed a higher prevalence of genetically determined dental anomalies such as increased molar bud distance, atypical position of tooth buds, congenital hypodontia, microdontia, delayed mineralization, delayed eruption, and atypical root shape in patients affected by mandibular prognathism than in other orthodontic patients.

The Class III malocclusion associated with mandibular height and prognathism has been described with the genes *ADAMTS1*, *ARHGAP21*, *GHR*, *Matrilin-1*, *EPB41*, *TGFB3*, *LTBP2*, *MYOIH*, and *KAT6B*, implying that molecular pathways involved in the development of bone (*TGFB3*, *LTBP*, *KAT6B*) and cartilage (*GHR*, *Matrilin-1*) may be implicated in mandibular size discrepancy.<sup>16,17,40,42–47</sup> Other candidate genes, *IGF1*, *HOXC*, *COL2A1*, and *DUSP6* have been associated not only for with mandibular prognathism, but also with maxillary deficiency.<sup>39,48,49</sup> Da Fontoura et al.<sup>35</sup> described the single-nucleotide polymorphisms in *FGFR2* and *COL1A1* as having a higher risk for skeletal Class III, and the *TBX5* gene as a reduced risk for this malocclusion.

Studies using principal component analysis and cluster analysis have been used to generate comprehensive

phenotypes and to identify the most homogeneous groups of Class III subjects. Moreno Uribe et al.<sup>16</sup> have identified 6 principal components that accounted for 81.2% of the variation, representing the variation of mandibular horizontal and vertical positions, maxillary horizontal position, and mandibular incisor angulation. In this study, the cluster model has identified 5 distinct subphenotypes of Class III malocclusion.<sup>16</sup> Another study, using the same multivariate method, has found similar findings; 5 clusters were identified with distinct subgroups of Class III malocclusion and the 5 principal components derived from the data explained 67% of the malocclusion variation. Their results suggested that different genes might be implicated in controlling dimensions vs structures.<sup>38</sup> These findings clearly demonstrated that Class III malocclusion exists in morphologically diverse patterns. Identifying these different phenotypes that can be related to different expressions of patient's genotype may assist in future genetic analyses, such as genotyping and linkage studies.

### Transversal Skeletal Malocclusion

The lack of transversal maxilla development and greater dental crowding have been associated with a polygenic multifactorial regulation and gene-environment interaction.<sup>20</sup> Cutroneo et al.<sup>50</sup> studied the integrin expression in masseter muscle specimens of severe Class III surgical patients with unilateral posterior cross bite of two or more posterior teeth. They remarked that the amount of integrins was significantly lower in muscle of the crossbite side than that observed in their counterpart. Their finding suggested that integrins may play a key role in the regulation of the masseter functional activity and may allow the optimization of contractile forces of this muscle. Whether the loss of regulatory effects on gene expression of these proteins will have an impact on the development of skeletal crossbite remains to be determined.

### Vertical Skeletal Malocclusion

Vertical skeletal malocclusions can be classified as skeletal open- or deep-bite, both presenting specific clinical characteristics. Skeletal open-bite is often associated with a negative overbite, hyper-divergence of the mandibular and palatal planes, increased anterior facial height, augmented clockwise facial growth, and proclined incisors.<sup>51</sup> The inverse features, such as an increased vertical overlap between the upper and lower incisors, short anterior lower face height, excessive forward rotation of the mandible, horizontal palatal plane and a large gonial angle characterize the skeletal deep-bite individuals.<sup>15,52</sup> The presence of open- or deep-bite in patients skeletal Class II and Class III are to some extent common.<sup>51,52</sup>

Two candidate genes, *PAX5* and *ABCA4-ARHGAP29*, have been associated with the vertical discrepancies ranging from skeletal deep to open bite.<sup>35</sup> Remarkably, the *ARHGAP29* gene has also been correlated with facial traits that are part of non-syndromic human cleft lip and/or palate.<sup>53</sup>

Genetic influences on the development of vertical malocclusions include heritable effects on both masticatory muscles and jaw morphology. Short and thin masseter muscles of low volume have been associated with dolichocephalic characteristics, such as open mandibular plane, a small posterior face

height and an increased gonial angle. Conversely, long and thick muscles of high volume were related to brachycephalic features.<sup>54</sup> The effect of the muscle will depend on the muscle thickness and the distribution of type I and II fibers.<sup>26</sup> Another example on how the masticatory muscle activity can influence skeletal structures is the development of open-bite malocclusion in patients with muscular dystrophy. Inversely, increases in the size and proportion of fast-contracting type II fibers in masticatory muscle has been shown to play an important influence on the development of skeletal deep-bite malocclusion. In fact, Huh et al.<sup>9</sup> have shown that genes for *HDAC4* and *KAT6B* that regulate histone acetylation to modify chromatin accessibility and transcription were both expressed at levels several fold greater in the deep-bite muscle and Class III malocclusion than in the open-bite muscle and Class II. According to Desh et al.<sup>40</sup> the association of *KAT6B* with mandibular prognathism can be correlated to its activation of the osteogenic transcription factor *RUNX2*, which is essential to bone growth and maintenance. Although they have also found a correlation of *RUNX2* expression with masseter muscle type II fibre, the role of this protein in adult mature muscle remains to be elucidated.

Another study of Zebrick et al.<sup>8</sup> demonstrated that the *ACTN3* is a gene that influences muscle performance and fiber type proportions. A common nonsense mutation, R577X identified in the *ACTN3* gene, results in a lack of alpha-actinin-3 protein expression. The loss of this protein has been shown to lead to smaller type II fiber diameters in masseter muscles and an increased expression of *ENPP1*, a negative regulator of mineralization. It has been demonstrated that the mutation *ACTN3* R577X is overrepresented in patients with skeletal Class II malocclusion, while its underrepresentation is observed in subjects with deep bite malocclusion, suggesting a biological influence during bone development and that muscle differences contribute to the vertical facial variation.

Interestingly, the vertical skeletal malocclusions have been associated with certain genetically determined dental anomalies. A study on the prevalence of palatally displaced maxillary canines observed a significant occurrence in patients with deep-bite and the hypodivergent phenotype, three times greater than in control subjects. No association with any other type of sagittal skeletal malocclusion has been identified. These authors concluded that a genetic component is associated with the aetiology of the palatal displacement of maxillary canines.<sup>55</sup> Another study on amelogenesis imperfecta (AI) has reported a frequent association with the skeletal open-bite malocclusion.<sup>56</sup> These authors have shown that the homozygous carriers of enamel (*ENAM*) mutation presented not only this dental anomaly, but also a Class II open-bite malocclusion. While some may believe that the coexistence of AI and open-bite malocclusion is the result of AI genes influencing the growth of the craniofacial skeleton, others may defend that dolichocephalic feature might be the result of the influence of modifying genes and/or environmental factors. Further studies are necessary to clarify whether the frequency occurrence of these dental disturbances in patients with vertical skeletal malocclusions is a mere coincidence or if there is in fact, a genetically aetiological association between these disorders.

## Sagittal Skeletal Malocclusion

Certain proteins encoded by specific genes may indirectly play a role in the development of skeletal malocclusions. For example, the myosin heavy chain (MYH) is an important contractile protein that is encoded by a group of genes consisting of I (slow) IIa, IIb, IIx (fast), extraocular, embryonic, and neonatal genes. Under stress, such as when the masseter muscle is stretched or compressed following orthognathic surgery for Class II and Class III, respectively, the MYH expression in the fibre is able to change from one phenotype into another. Breuel et al.<sup>57</sup> have showed significant difference in the levels of MYH8, MYH1, and FOXO3a between Class II patients and Class III patients, six months after orthognathic surgery. Most Class II subjects presented with continuing masseter atrophy following surgery and a delayed conversion of the type of fibre with the lengthening of the mandible. This evidence suggests that the genetic response to the neuromuscular adaptation of the masticatory muscle could explain the high relapse of the malocclusion following orthosurgery treatment.

## ROLE OF EPIGENETICS ON MALOCCLUSION

The epigenetic regulation has been suggested to play a fundamental role in the entire masticatory musculoskeletal complex during the development of a malocclusion.<sup>9</sup> A better understanding of epigenetic factors and the mechanisms that determine gene expression is essential to clarify how genetic influences contribute to growth and to the diversity of facial phenotypes.

Among potential genes implicated in growth development, the homeobox genes are known to play a role in patterning embryonic development and considered to be the master genes of the head and face.<sup>5,58</sup> Transcription factors, such as Hox group, muscle segment (*Msx1* and *Msx2*), *dustakless* (*Dlx*), orthodontical (*Otx*), *gooseoid* (*Gsc*), and *sonic hedgehog* (*Shh*) are responsible for activating or suppressing gene expression, which in conjunction with other genes, activate a cascade of events leading to the control of patterning and morphogenesis.<sup>59</sup> Two major family groups of regulatory proteins, mesenchymal growth factors, bone morphogenetic proteins and the steroid/thyroid/retinoic acid, are vehicles through which the information of these genes is expressed. These mechanisms are of particular interest in research of craniofacial biology and development because they allow a better understanding of the process involved in jaw size discrepancies and/or dysmorphogenesis.

While it is undeniable that some facial structures, such as the basic form of the mandibular body, the location of the nasal capsule, the size of the teeth and the arch shape are under direct genetic influence,<sup>5,24</sup> it has been largely recognized that the growth and the final morphology of the dentofacial structures is determined by the impact of the environmental factors.<sup>5,26</sup> In fact, the craniofacial size and shape are determined by a complex interaction of both genetic and environmental factors and the maxillary and mandibular discrepancies are a distinctive niche on this gene-environment dynamic spectrum. A typical example of this genetic-environment interaction is the soft tissue. Although its morphology has been considered

to be primarily genetically determined, its behavior is influenced by both genetic and environment factors. For example, the environmental factors disrupt resting oral posture, which in turn, increases the vertical skeletal growth leading to a dental malocclusion. Occlusal characteristics are primarily defined by inherited muscle patterns, including the muscle patterns of the tongue.<sup>26</sup> The occlusion and skeletal alterations are of multifactorial etiology,<sup>10</sup> and the relative contributions of genetic and environmental may explain the phenotypic variation. Some believe that the phenotypic occlusal variations are mostly caused by environmental differences rather than due to the polygenic mode of inheritance, although there is no strong evidence for this.<sup>6,60</sup>

A study of Fraga et al.<sup>27</sup> involving a large cohort of monozygotic twins examined the global and locus specific differences in their DNA methylation and histone acetylation. They observed that while young twins were epigenetically indistinguishable on the early years of life, older twins demonstrated remarkable differences in DNA methylation and histone modification, showing an important impact on their gene expression. These epigenetic markers were more evident in older monozygotic twins who had different lifestyles and have spent less of their lives together, evidencing the significant role of environmental factors in translating a common genotype into a diverse phenotype. Evident to say that studies in the epigenetic field are essential to allow us to have a better understanding of how different phenotypes of skeletal Class II and Class III, as earlier described, can originate from the same genotype.

The polygenic systems may have the capacity to protect developmental processes against any hostile environmental influence. However, when a substitution of deleterious genes decreases this protection beyond the level where environmental factors may be counterweighed, a skeletal developmental defect might result, such as cleft lip and palate and facial asymmetry.<sup>5</sup> A developmental disarrangement between these genetic-environmental interactions may explain not only craniofacial abnormalities, but also can help us to better comprehend the regulation of maxillary, mandibular and tooth morphologies.

## CLINICAL APPLICATIONS AND CONCLUSION

Preliminary studies suggest that orthodontic treatments may be effective for pediatric obstructive sleep apnea,<sup>61–63</sup> thereby possibly reducing the incidence later in adulthood: up to 70% of adults with sleep apnea snored during childhood.<sup>64</sup> Orthodontic therapy can successfully treat skeletal jaw discrepancies by modifying the direction of dentofacial growth<sup>25</sup> and therefore, changing the phenotype of a specific morphogenetic pattern. However, the treatment success rate depends on several factors, including the contribution of gene-environmental interaction to the malocclusion and the capacity of the orthodontic and orthopaedic appliances to modify the skeletal pattern. Still, it is unknown whether it is possible to influence the skeletal bases beyond their genetically predetermined potential.<sup>22,65</sup> The greater the genetic component, the lower the rate of success on the outcome of orthodontic treatment. For example, if the cause of a severe mandibular prognathism is primary genetic, the treatment is considered to be

only palliative and an orthognathic surgery is required. The real therapy should be an eventual modification of the gene responsible for the mandibular prognathism, however this is yet a theoretical proposition. Nevertheless, the identification of major genes and determination of their biochemical action to a particular jaw discrepancy is the first approach necessary for the search of a solution.<sup>3</sup>

Further studies with randomized clinical trials on longitudinal cohorts of patients treated with different treatment approaches and also, genetic mapping and statistical techniques to family and twin data are the pathways to clarify the interaction of genotype and environment on the maxillo-mandibular discrepancies.<sup>12</sup> If a precise skeletal malocclusion is influenced mostly by environmental factors, the objective would be then to identify the mainly cause and intercept the harmful influence on the normal development of the dentofacial structures.<sup>21,31</sup> However, the challenge remains on how to determine the contribution of genetic and environmental factors in a specific skeletal malocclusion.

Early detection of the consequences of abnormal craniofacial development and assessment of orthodontic practices will validate the treatments used, establish practice parameters, and change the natural history of pediatric obstructive sleep apnea, thereby possibly preventing or delaying the development of sleep apnea in adulthood. With the advent of diagnostic techniques in the field of molecular genetics, the orthodontic treatment may take on a completely new direction. Such technological advances may open doors for the development of molecular approach to develop better strategies for the diagnostic, prevention and facilitate treatment modalities.<sup>65,66</sup>

## REFERENCES

- Johal A, Patel SI, Battagel JM. The relationship between craniofacial anatomy and obstructive sleep apnoea: a case-controlled study. *J Sleep Res* 2007;16:319–26.
- Lee RW, Chan AS, Grunstein RR, Cistulli PA. Craniofacial phenotyping in obstructive sleep apnea—a novel quantitative photographic approach. *Sleep* 2009;32:37–45.
- Smith R, Bailit H. Problems and methods in research on the genetics of dental occlusion. *Angle Orthod* 1977;47:65–77.
- Normando D, Faber J, Guerreiro J, Quintao C. Dental occlusion in a split Amazon indigenous population: genetics prevails over environment. *PLoS One* 2011;6:e28387.
- Mossey P. The heritability of malocclusion: part I—genetics, principles and terminology. *Br J Orthod* 1999;26:103–13.
- Corruccini RS, Townsend GC, Richards LC, Brown T. Genetic and environmental determinants of dental occlusal variation in twins of different nationalities. *Hum Biol* 1990;62:353–67.
- Chung CS, Niswander JD, Runck DW, Bilben SE, Kau MC. Genetic and epidemiologic studies of oral characteristics in Hawaii's schoolchildren. II. Malocclusion. *Am J Hum Genet* 1971;23:471–95.
- Zebrick B, Teeramongkolgul T, Nicot R, et al. ACTN3 R577X genotypes associate with Class II and deepbite malocclusions. *Am J Orthod Dentofacial Orthop* 2014;146:603–11.
- Huh A, Horton M, Cuenco K, et al. Epigenetic influence of KAT6B and HDAC4 in the development of skeletal malocclusion. *Am J Orthod Dentofacial Orthop* 2013;144:568–76.
- Hughes T, Thomas C, Richards L, Townsend G. A study of occlusal variation in the primary dentition of Australian twins and singletons. *Arch Oral Biol* 2001;46:857–64.
- Goodman HO. Genetic parameters of dentofacial development. *J Dent Res* 1965;44:174–84.



12. Lovelina FD, Shastri SM, Kumar PD. Assessment of the oral health status of monozygotic and dizygotic twins - a comparative study. *Oral Health Prev Dent* 2012;10:135–9.
13. Meister M, Masella RS. Field of dreams. *Am J Orthod Dentofacial Orthop* 2003;123:352–3.
14. Roedig J, Phillips B, Morford L, et al. Comparison of BMI, AHI, and apolipoprotein E ε4 (APOE-ε4) alleles among sleep apnea patients with different skeletal classifications. *J Clin Sleep Med* 2014;10:397–402.
15. Proffit W, Fields H, Sarver D. *Contemporary orthodontics*. St. Louis, MO: Mosby Elsevier, 2013.
16. Moreno Uribe LM, Vela KC, Kummet C, Dawson DV, Southard TE. Phenotypic diversity in white adults with moderate to severe Class III malocclusion. *Am J Orthod Dentofacial Orthop* 2013;144:32–42.
17. Moreno Uribe LM, Howe SC, Kummet C, Vela KC, Dawson DV, Southard TE. Phenotypic diversity in white adults with moderate to severe Class II malocclusion. *Am J Orthod Dentofacial Orthop* 2014;145:305–16.
18. Thilander B, Pena L, Infante C, Parada SS, de Mayorga C. Prevalence of malocclusion and orthodontic treatment need in children and adolescents in Bogota, Colombia. An epidemiological study related to different stages of dental development. *Eur J Orthod* 2001;23:153–67.
19. Borzabadi-Farahani A, Borzabadi-Farahani A, Eslamipour F. Malocclusion and occlusal traits in an urban Iranian population. An epidemiological study of 11- to 14-year-old children. *Eur J Orthod* 2009;31:477–84.
20. Mossey P. The heritability of malocclusion: part 2. The influence of genetics in malocclusion. *Br J Orthod* 1999;26:195–203.
21. Kawala B, Antoszevska J, Necka A. Genetics or environment? A twin-method study of malocclusions. *World J Orthod* 2007;8:405–10.
22. Lobb W. Craniofacial morphology and occlusal variation in monozygous and dizygous twins. *Angle Orthod* 1987;57:219–33.
23. Cruz RM, Krieger H, Ferreira R, Mah J, Hartsfield J Jr., Oliveira S. Major gene and multifactorial inheritance of mandibular prognathism. *Am J Med Genet A* 2008;146A:71–7.
24. Martha K, Zetu I, Ogodescu A, Gyergay R, Kovacs S. Study of dental and skeletal disorders in mono- and dizygotic twins. *Rev Med Chir Soc Med Nat Iasi* 2014;118:199–204.
25. Dudas M, Sassouni V. The hereditary components of mandibular growth, a longitudinal twin study. *Angle Orthod* 1973;43:314–22.
26. Mew JR. The postural basis of malocclusion: a philosophical overview. *Am J Orthod Dentofacial Orthop* 2004;126:729–38.
27. Fraga MF, Ballestar E, Paz MF, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci U S A* 2005;102:10604–9.
28. Horowitz S, Osborne R, DeGeorge F. A cephalometric study of craniofacial variation in adult twins. *Angle Orthod* 1960;30:1–5.
29. Chou S, Tseng Y, Pan C, Chang J, Chang H. Craniofacial skeletal dysplasia of opposite-sex dizygotic twins. *J Formos Med Assoc* 2011;110:342–6.
30. Padure H, Negru AR, Stanciu D. The class II/1 anomaly of hereditary etiology vs. thumb-sucking etiology. *J Med Life* 2012;5:239–41.
31. Varrel J, Alanen P. Prevention and early treatment in orthodontics: a perspective. *J Dent Res* 1995;74:1436–8.
32. Gutierrez SJ, Gomez M, Rey JA, Ochoa M, Gutierrez SM, Prieto JC. Polymorphisms of the noggin gene and mandibular micrognathia: a first approximation. *Acta Odontol Latinoam* 2010;23:13–9.
33. Nieto MA. The snail superfamily of zinc-finger transcription factors. *Nat Rev Mol Cell Biol* 2002;3:155–66.
34. Murray SA, Oram KF, Gridley T. Multiple functions of Snail family genes during palate development in mice. *Development* 2007;134:1789–97.
35. da Fontoura CS, Miller SF, Wehby GL, et al. Candidate gene analyses of skeletal variation in malocclusion. *J Dent Res* 2015;94:913–20.
36. Basdra E, Kiokpasoglou M, Stellzig A. The Class II Division 2 craniofacial type is associated with numerous congenital tooth anomalies. *Eur J Orthod* 2000;22:529–35.
37. Thompson E, Winter R. Another family with the 'Habsburg jaw'. *J Med Genet* 1988;25:838–42.
38. Bui C, King T, Proffit W, Frazier-Bowers S. Phenotypic characterization of Class III patients. *Angle Orthod* 2006;76:564–9.
39. Nikopensius T, Saag M, Jagomägi T, et al. A missense mutation in DUSP6 is associated with Class III malocclusion. *J Dent Res* 2013;92:893–98.
40. Desh H, Gray SL, Horton MJ, et al. Molecular motor MYO1C, acetyltransferase KAT6B and osteogenetic transcription factor RUNX2 expression in human masseter muscle contributes to development of malocclusion. *Arch Oral Biol* 2014;59:601–7.
41. Stahl F, Kopp H, Feldmann H, Grabowski R. Epidemiology of Hoffmeister's genetically determined predisposition to disturbed development of the dentition in patients with true skeletal class III malocclusion. *J Orofac Orthop* 2005;66:6–19.
42. Guan X, Song Y, Ott J, et al. The ADAMTS1 Gene Is Associated with Familial Mandibular Prognathism. *J Dent Res* 2015;94:1196–201.
43. Tassopoulou-Fishell M, Deeley K, Harvey EM, Sciote J, Vieira AR. Genetic variation in myosin 1H contributes to mandibular prognathism. *Am J Orthod Dentofacial Orthop* 2012;141:51–9.
44. Xue F, Wong R, Rabie AB. Identification of SNP markers on 1p36 and association analysis of EPB41 with mandibular prognathism in a Chinese population. *Arch Oral Biol* 2010;55:867–72.
45. Zhou J, Lu Y, Gao X, et al. The growth hormone receptor gene is associated with mandibular height in a Chinese population. *J Dent Res* 2005;84:1052–6.
46. Li Q, Li X, Zhang F, Chen F. The identification of a novel locus for mandibular prognathism in the Han Chinese population. *J Dent Res* 2011;90:53–7.
47. Perillo L, Monsurro A, Bonci E, Torella A, Mutarelli M, Nigro V. Genetic association of ARHGAP21 gene variant with mandibular prognathism. *J Dent Res* 2015;94:569–76.
48. Xue F, Rabie AB, Luo G. Analysis of the association of COL2A1 and IGF-1 with mandibular prognathism in a Chinese population. *Orthod Craniofac Res* 2014;17:144–9.
49. Frazier-Bowers S, Rincon-Rodriguez R, Zhou J, Alexander K, Lange E. Evidence of linkage in a Hispanic cohort with a Class III dentofacial phenotype. *J Dent Res* 2009;88:56–60.
50. Cutroneo G, Piacino MG, Ramieri G, et al. Expression of muscle-specific integrins in masseter muscle fibers during malocclusion disease. *Int J Mol Med* 2012;30:235–42.
51. Arriola-Guillén L, Flores-Mir C. Molar heights and incisor inclinations in adults with Class II and Class III skeletal open-bite malocclusions. *Am J Orthod Dentofacial Orthop* 2014;145:325–32.
52. Huang GJ, Bates SB, Ehlert AA, Whiting DP, Chen SS, Bollen AM. Stability of deep-bite correction: a systematic review. *J World Fed Orthod* 2012;1:e89–e96.
53. Miller S, Weinberg S, Nidey N, et al. Exploratory genotype-phenotype correlations of facial form and asymmetry in unaffected relatives of children with non-syndromic cleft lip and/or palate. *J Anat* 2014;224:688–709.
54. Benington P, Gardener J, Hunt N. Masseter muscle volume measured using ultrasonography and its relationship with facial morphology. *Eur J Orthod* 1999;21:659–70.
55. Sacerdoti R, Baccetti T. Dentoskeletal features associated with unilateral or bilateral palatal displacement of maxillary canines. *Angle Orthod* 2004;74:725–32.
56. Hart TC, Hart PS, Gorry MC, et al. Novel ENAM mutation responsible for autosomal recessive amelogenesis imperfecta and localised enamel defects. *J Med Genet* 2003;40:900–6.
57. Breuel W, Krause M, Schneider M, Harzer W. Genetic stretching factors in masseter muscle after orthognathic surgery. *Br J Oral Maxillofac Surg* 2013;51:530–5.
58. Zernik J, Minken C. Genetic control of bone remodeling. *J Calif Dent Assoc* 1992;20:14–9.
59. Thesleff I. Homeobox genes and growth factors in regulation of craniofacial and tooth morphogenesis. *Acta Odontol Scand* 1995;53:129–34.
60. Cassidy KM, Harris EF, Tolley EA, Keim RG. Genetic influence on dental arch form in orthodontic patients. *Angle Orthod* 1998;68:445–54.

61. Villa MP, Rizzoli A, Rabasco J, et al. Rapid maxillary expansion outcomes in treatment of obstructive sleep apnea in children. *Sleep Med* 2015;16:709–16.
62. Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion (RME) for pediatric obstructive sleep apnea: a 12-year follow-up. *Sleep Med* 2015;16:933–5.
63. Pirelli P, Saponara M, Guilleminault C. Rapid maxillary expansion in children with obstructive sleep apnea syndrome. *Sleep* 2004;27:761–6.
64. Guilleminault C, Dement WC. Sleep apnea syndromes and related sleep disorders. In: Williams R, Karacan I, eds. *Sleep apnea syndromes and related sleep disorders*. AR Liss, 1978:13–6.
65. Carlson DS. Biological rationale for early treatment of dentofacial deformities. *Am J Orthod Dentofacial Orthop* 2002;121:554–8.
66. D'Souza RN, Dunnwald M, Frazier-Bowers S, et al. Translational genetics: advancing fronts for craniofacial health. *J Dent Res* 2013;92:1058–64.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication December, 2015  
 Submitted in final revised form December, 2015  
 Accepted for publication January, 2016  
 Address correspondence to: Clarice Nishio, DDS, MSc, PhD, Faculty of Dentistry, University of Montreal, 3525 Chemin Queen-Mary, Montreal, Quebec, Canada, H3V 1H9; Tel: (514) 343-2469; Fax: (1-514) 343-2233; Email: clarice.nishio@umontreal.ca

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest.



# Maxillomandibular Advancement Surgery as a Treatment of Obstructive Sleep Apnea in a Patient with Cleidocranial Dysostosis: A Case Report

Heather Chance, DMD; Lee Pollan, DMD, MS

Oral and Maxillofacial Surgery, University of Rochester, Rochester, NY

**STUDY OBJECTIVES:** Maxillomandibular advancement surgery is a well-supported treatment option for obstructive sleep apnea in patients who have not responded to or who have not tolerated nonsurgical management. The usual straightforward surgical procedure can be made much more difficult with numerous impacted supernumerary teeth, as is frequently seen in patients with cleidocranial dysostosis.

**METHODS:** The preoperative planning, surgical procedure, and postoperative phase of the maxillomandibular advancement surgery for a 51-year-old patient with severe OSA (apnea-hypopnea index 94 events/h in 2010) and concomitant cleidocranial dysostosis will be discussed in this case report.

**RESULTS:** When compared to the preoperative polysomnographic examination, striking improvements were noted on the examination at 8 months after surgery (apnea-hypopnea index from 94 to 21 events/h).

**CONCLUSIONS:** The results of this case showed that using traditional maxillomandibular advancement surgical protocols, despite the numerous impacted supernumerary teeth, provides excellent results for the treatment of severe OSA. The patient will require further follow-up and likely subsequent treatment of his remaining dentition.

**KEYWORDS:** obstructive sleep apnea, cleidocranial dysplasia, telegnathic surgery, maxillomandibular surgery

**CITATION:** Chance H, Pollan L. Maxillomandibular advancement surgery as a treatment of obstructive sleep apnea in a patient with cleidocranial dysostosis: a case report. *Journal of Dental Sleep Medicine* 2016;3(2):65–70.

## INTRODUCTION

Obstructive sleep apnea (OSA) is characterized by intermittent but prolonged upper airway obstruction that disrupts normal ventilation during sleep.<sup>1</sup> It is often associated with daytime somnolence, neurocognitive deficits, and an increased risk of cardiovascular events which leads to overall increased morbidity and mortality.<sup>2</sup> The American Academy of Sleep Medicine classifies severity of OSAS based on the mean number of apneas and hypopneas per hour during sleep (AHI).<sup>3</sup> Mild between 5 and 15, moderate 15–30, and severe greater than 30.<sup>4</sup>

Cleidocranial dysostosis is an autosomal dominant congenital defect that involves the development of the teeth and bones. It is thought to involve the *RUNX2* gene which is responsible for making a protein involved in cartilage and bone development and maintenance.<sup>5</sup> Without the functioning gene, individuals with cleidocranial dysostosis may have osteopenia, underdeveloped or absent clavicles, delayed closure of the fontanels, and short stature. In terms of the facial skeleton, brachycephaly, frontal bossing, and hypertelorism are common. Dental abnormalities including delayed exfoliation of primary teeth, delayed eruption of the permanent dentition, malformed teeth, malocclusion, and multiple supernumerary teeth. In addition, many patients with cleidocranial dysostosis present with hearing loss and increased incidence of ear and sinus infections.<sup>6</sup>

There is no current evidence to suggest a link between OSA and cleidocranial dysostosis and the treatment of a patient with both may present a challenge to the treating surgeon.

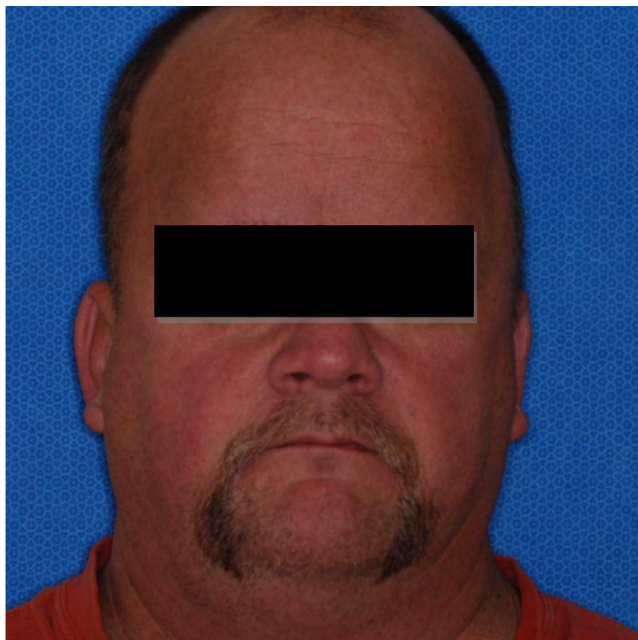
With the typical presentation of multiple impacted supernumerary teeth, both the actual maxillomandibular advancement surgical osteotomies and fixation have the potential to be much more difficult.

## REPORT OF CASE

A 51-year-old man with known cleidocranial dysostosis and obstructive sleep apnea presented to the University of Rochester, Strong Memorial Hospital Oral and Maxillofacial Surgery clinic for surgical evaluation. He was diagnosed with extremely severe OSA 7 years earlier (2006), with a polysomnographic examination that showed an apnea-hypopnea index (AHI) = 84 episodes/h; time of sleep with SpO<sub>2</sub> < 90% = 17 min (5%); total sleep time (TST) = 347 min. At that point, he was treated with a CPAP that he was, unfortunately, unable to tolerate. He had a second polysomnographic examination in 2010 which again revealed extremely severe OSA with an (AHI) = 94 episodes/h; time of sleep with SpO<sub>2</sub> < 90% = 135 min (49.8%); total sleep time (TST) = 313 min. The patient reported multiple episodes of falling asleep while driving and has had several minor motor vehicle accidents as a result. He has a past medical history significant for mild GERD, controlled hypertension, angina pectoris, and congestive heart failure (ejection fraction = 35%). He reported an untreated depression and felt that his constant feeling of fatigue was related.

The general physical examination revealed a well-nourished, well developed patient with a BMI on initial presentation of



**Figure 1**—Preoperative facial photograph, lateral view.**Figure 2**—Preoperative facial photograph, frontal view.**Figure 3**—Preoperative intraoral photograph, frontal view in occlusion.**Figure 4**—Preoperative orthopantomogram radiograph.

37.9. He was, at that time, enrolled in a weight loss program. He presented with a flat profile, frontal bossing, and sunken nasal bridge. He had some degree of hearing loss bilaterally, present since birth. He had no nasal or sinus complaints, no soft palate, tonsillar, or tongue base hypertrophy though he did present with a Mallampati III airway with a maximum incisal opening of approximately 28 mm (**Figures 1** and **2**). He had multiple palpable and multiple non-palpable impacted teeth. The only erupted teeth present intraorally were teeth numbers 4, 5, 12,

21, 28, and primary teeth C, F, H, M, N, O, P, Q, R therefore there was no measurable occlusion (**Figure 3**).

A panoramic radiograph (**Figure 4**) revealed fully impacted teeth #1, 2, 6, 7, 8, 9, 10, 11, 15, 16, 17, 18, 19, 22, 23, 24, 25, 26, 27, and 32. The ascending ramus are slightly narrow and the coronoid processes thin and pointed.

Lateral cephalogram (**Figure 5**) revealed a hypoplastic maxilla and mandible, and an obtuse mandibular plane angle (76.3 degrees, normal 65). Relative airway restriction in the anterior and posterior dimension is also visualized. Computed tomography (CT) scan obtained while the patient was entirely conscious, revealed narrowed upper airway space as well (**Figure 6**).

Due to the occlusal findings, the traditional orthognathic acrylic splint fabrication was difficult. Using the 14 teeth that were erupted with only 4 actually in occlusion, both the interim and final acrylic splints were made using these contacts as well as full contact with the attached gingival overly both the upper and lower alveolus. With so few erupted teeth, both preoperative orthodontics and intraoperative archbars were not possible for stabilization of the splints and the arches in their new position. Thus, intermaxillary fixation screws were planned for intraoperative stabilization.

Surgical treatment was performed under general anesthesia using a nasal endotracheal tube. Intermaxillary screws were placed first; 4 in the maxilla and 4 in the mandible, all 8 mm in length. The traditional horizontal incision and osteotomy were performed at the LeFort 1 level. As per usual surgical protocol, a double guarded nasal osteotome was used to separate the nasal



septum from the nasal crest of the maxilla. The single guarded osteotome was then used to separate the lateral nasal wall/medial maxillary sinus wall. A small, then large, curved osteotome was used to separate the maxilla from the pterygoid plates, and a Rowe disimpaction forceps was used to disimpact that maxilla. Given the location of the multiple supernumerary teeth, many were included in the osteotomy and left in place. The interim acrylic splint was placed into the mouth and wired in place using the intermaxillary fixation wires. After adjusting and enlarging the piriform aperture, the maxilla was held up and into the final planned position, 10 millimeters anterior to the preoperative position, and secured with 4 L-shaped mini plates and 16 six-millimeter screws. The interim splint was removed and the maxilla was found to be stable in the new position.

The surgery was continued with bilateral sagittal split osteotomy of the mandible. Once again, the traditional approach and osteotomies were used. A proper split was obtained bilaterally and both the inferior alveolar nerve and full bony impacted teeth #17 and 32 were visualized and free of trauma. Given the highly impacted nature of these impacted teeth and the expected subsequent weakening of the mandible, they were left in place. After the final acrylic splint was placed and intermaxillary fixation was complete, the mandible was advanced 10 millimeters and fixated in place using 3 bicortical screws on the superior aspect of the mandible placed transcutaneously using a trocar. The intermaxillary fixation wires and intermaxillary fixation screws were removed in totality. The patient was advised to follow a liquid diet protocol during the 5 weeks postoperatively then was to resume normal diet.

The patient reported feeling more rested with less daytime somnolence within the first week postoperatively. He continued to improve over the first several weeks and transitioned easily from full liquid diet to solids as instructed. He reported easily working 12-hour shifts without the fatigue he used to feel prior to surgery. His mood was elevated and his outlook on life more positive. Clinically he appeared to be well-healed from a surgical standpoint, with no mobility of the segments, no mucosal dehiscence, no signs or symptoms of active infection. His postoperative radiographs revealed stable hardware and no acute or chronic complications of the teeth in the line of osteotomy (Figures 7–12).

On follow-up polysomnogram, done December 2013, the AHI dropped down to 21 episodes per hour of sleep, with only 3 minutes 45 seconds with an oxygen saturation below 90%, and a total sleep time (TST) of 394 minutes (Table 1).

## DISCUSSION

It is well documented in the literature that maxillomandibular advancement (MMA) surgery increases anterior-posterior and medial-lateral airway size, which can help improve or eliminate OSA.<sup>7,8</sup> In 2013, Sittitavornwong et al. demonstrated that, independent of age or gender, all patients who underwent MMA, showed an increase in airway cross-sectional area and a decrease in the pressure effort at every airway level after MMA. In general, as the airway obstruction worsens, a greater pressure effort is required to inspire a normal volume of air. Increasing the 3-dimensional airway space, should decrease

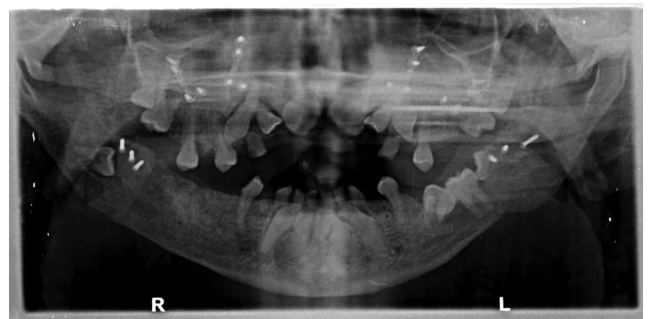
**Figure 5**—Preoperative lateral cephalometric radiograph.



**Figure 6**—Preoperative CT, axial view of airway.

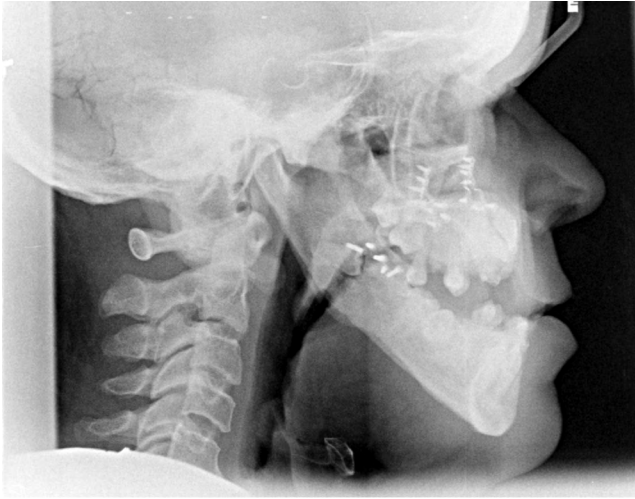


**Figure 7**—Postoperative orthopantomogram radiograph.



this pressure effort, thus decreasing the work of breathing.<sup>9</sup> By changing the skeletal framework, MMA increases the pharyngeal space, pulling the tongue and suprahyoid muscles

**Figure 8**—Postoperative lateral cephalometric radiograph.



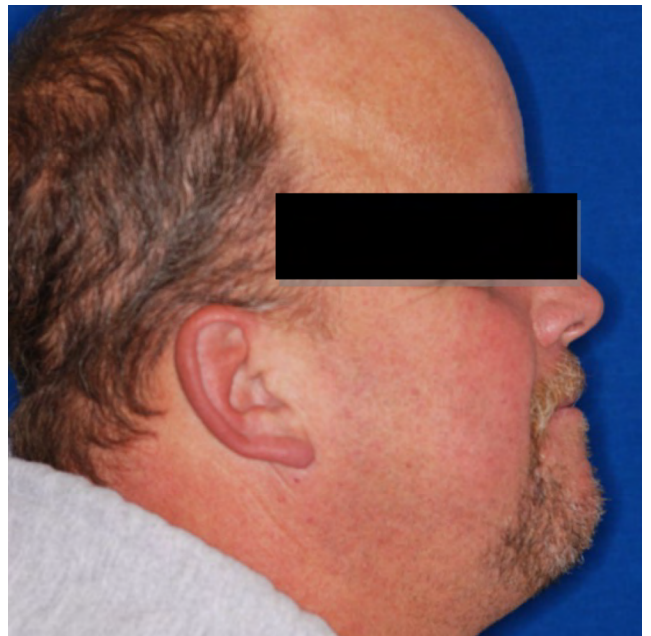
**Figure 9**—Postoperative posterior-anterior skull radiograph.



**Figure 10**—Postoperative facial photograph, frontal view.



**Figure 11**—Postoperative facial photograph, lateral view.



**Table 1**—Comparison of preoperative and postoperative sleep study measures.

Measurements	09/11/2006	07/22/2010	12/06/2013
Total sleep time	347 min	313 min	351 min
Respiratory events	485	125	14
AHI	84	94	21.4
Time saturation < 90%	17 min, 23 sec	14 min, 56 sec	3 mins, 45 sec



**Figure 12**—Postoperative intraoral photograph, frontal view in occlusion.



anteriorly. It is currently felt to be the most effective surgical technique for the treatment of obstructive sleep apnea.<sup>10,11</sup>

There is a significant evidence that early treatment of the dental signs of cleidocranial dysostosis, including multiple supernumerary teeth, malformed dentition, and failure of eruption of teeth, is beneficial to both the aesthetics and long-term functionality of patients.<sup>12,13</sup> Extraction of supernumerary teeth, exposure of impacted teeth with traction and orthodontics can lead to a stable long-term occlusion when patients are treated in the prepubescent and early teen years.<sup>14</sup>

A direct cause and effect link between cleidocranial dysostosis and obstructive sleep apnea has never been established. It does not seem that OSAS is one of the clinical manifestations of the syndrome. Age, gender, and certainly obesity are all well documented to be correlated with OSA.<sup>15-17</sup> The prevalence of moderate or severe OSA in the elderly has been reported in the 7% to 44% range, with a much lower influence from BMI/obesity.<sup>18</sup> In the Caucasian population, the cutoff value of BMI for obesity is 30 kg/m<sup>2</sup>, and has been reported as low as 23 kg/m<sup>2</sup> in some Asian-Indian populations.<sup>19</sup> With the aging population and increasing obesity prevalence, we will certainly see an overall increase in OSAS, including patients born with cleidocranial dysostosis. In patients with cleidocranial dysostosis that have been treated with early intervention for the supernumerary, malformed, and impacted teeth, the traditional maxillomandibular advancement surgery approach would be simple to apply. In those patients that have not previously been treated and present with many unerupted teeth and without a stable occlusion, the surgical planning can be complicated. As seen in this case report, maxillomandibular advancement surgery via the conventional approach, leaving the unerupted teeth within the osteotomy sites both during downfracture/sagittal split and during fixation, can be effective in treating and improving severe OSA.

## CONCLUSION

In the setting of severe obstructive sleep apnea, cleidocranial dysostosis is not a contraindication for maxillomandibular advancement surgery, even with the presence of multiple impacted and missing teeth.

## REFERENCES

1. Malhotra A, White DP. Obstructive sleep apnea. *Lancet* 2002;360:237–45.
2. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population healthy perspective. *Am J Respir Crit Care Med* 2002;165:1217–39.
3. Doff M, Jansma J, Schepers R, Hoekema A. Maxillomandibular advancement surgery as alternative to continuous positive airway pressure in morbidly severe obstructive sleep apnea: a case report. *J Craniomandib Sleep Pract* 2013;31:246–51.
4. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. *Sleep* 1999;22:667–89.
5. National Library of Medicine (US). Genetics Home Reference. Cleidocranial Dysplasia. Reviewed January 2008. Accessed Nov. 14, 2014. Available from: <http://ghr.nlm.nih.gov/condition/cleidocranial-dysplasia>.
6. Pagon RA, Adam MP, Ardinger HH, et al. GeneReviews, Cleidocranial Dysplasia. Seattle, WA: University of Washington, 1993–2015.
7. Schendel S, Broujerdi J, Jacobson R. Three-dimensional upper-airway changes with maxillomandibular advancement for obstructive sleep apnea treatment. *Am J Orthod Dentofacial Orthop* 2014;146:385–93.
8. Bianchi A, Betti E, Tarsitano A, Morselli-Labate AM, Lancellotti L, Marchetti C. Volumetric three-dimensional computer tomographic evaluation of the upper airway in patients with obstructive sleep apnea syndrome treated by maxillomandibular advancement. *Br J Oral Maxillofac Surg* 2014;52:831–7.
9. Sittitavornwong S, Waite P, Shih A, et al. Computational fluid dynamic analysis of the posterior airway space after maxillomandibular advancement for obstructive sleep apnea syndrome. *J Oral Maxillofac Surg* 2013;71:397–405.
10. Li K. Surgical management of obstructive sleep apnea. *Clin Chest Med* 2003;24:365–70.
11. Butterfield KJ, Marks PL, McLean L, Newton J. Pharyngeal airway morphology in healthy individuals and in obstructive sleep apnea patients treated with maxillomandibular advancement: a comparative study. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2015;119:285–92.
12. Balaton G, Tarjan I, Balaton P, Barabasi Z, Gyulai G, Nagy K, Vajo Z. Orthodontic and oral surgery therapy in cleidocranial dysplasia. *Fogory Sz* 2007;100:17–21.
13. Mortellaro C, Greco L, Prota E. Differing therapeutic approaches to cleidocranial dysplasia (CCD). *Minerva Stomatol* 2012;61:155–63.
14. Zhang CY, Si Y, Wang XZ, Sun XY, Yan WJ, Zheng SG. Early dental treatments for patients with cleidocranial dysplasia. *Chin J Dent Res* 2014;18:51–7.
15. Bixler EO, Vgontzas AN, Ten Have T, Tyson K, Kales A. Effects of age on sleep apnea in men. *Am J Respir Crit Care Med* 1998;157:144–8.
16. Dancy DR, Hanly PJ, Soong C, Lee B, Shepard J Jr, Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. *Chest* 2003;123:1544–50.
17. Romero-Corral A, Caples SM, Lopez-Jimenez F, Somers VK. Interactions between obesity and obstructive sleep apnea: implications for treatment. *Chest* 2010;137:711–9.
18. Duran J, Esnaola S, Rubio R, Iztueta A. Obstructive sleep apnea-hypopnea and related clinical features in a population-based sample of subjects aged 30 to 70 yr. *Am J Respir Crit Care Med* 2001;163:685–9.
19. Snehalatha C, Viswanathan V, Ramachandran A. Cutoff values for normal anthropometric variables in Asian Indian adults. *Diabetes Care* 2003;26:1380–4.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication November, 2015

Accepted for publication February, 2016

Address correspondence to: Heather Chance, DMD, 5318 NC Hwy 55, Suite 106, Durham, NC 27713; Tel: (919) 806-2912; Fax: (919) 806-2915

## **DISCLOSURE STATEMENT**

This was not an industry supported study. The authors have indicated no financial conflicts of interest. Case Report performed at the University of Rochester, Strong Memorial Hospital

# A Case of Polysomnographic Changes Using a Twin-Block Appliance in a Child with Maxillary Protrusion

Hisashi Hosoya, DDS, PhD; Kawanabe Hitoshi, DDS, PhD; Fukui Kazunori, DDS, PhD

Division of Orthodontics and Dentofacial Orthopedics, School of Dentistry, Ohu University, Fukushima, Japan

A 9-year-old male presented with Angle CL II Div 1, a retruded mandible, and suspected obstructive sleep apnea (OSA). We planned to treat the mandibular protrusion with a twin-block appliance (TB). We examined craniofacial morphology and sleep-disordered breathing (oxygen saturation [SpO<sub>2</sub>] and oxygen desaturation index [ODI]) changes at three different time periods using cephalometric radiographs and pulse oximeters. The areas in the oropharynx and hypopharynx increased at the start of the TB treatment. With the pulse oximeter, the 2%, 3%, and 4% ODI readings decreased at the treatment start; however, SpO<sub>2</sub> increased only after 6 months.

**KEYWORDS:** child OSAS, twin-block appliance, sleep disordered breathing, skeletal pattern, orthodontics

**CITATION:** Hosoya H, Hitoshi K, Kazunori F. A case of polysomnographic changes using a twin-block appliance in a child with maxillary protrusion. *Journal of Dental Sleep Medicine* 2016;3(2):71–72.

## INTRODUCTION

In previous studies, obstructive sleep apnea (OSA) has been associated with impaired growth hormone secretion in children.<sup>1</sup> Adenoid hypertrophy, hypertrophic or allergic rhinitis, and posterior deviation of the maxilla or mandible are all risk factors for childhood OSA.<sup>2</sup> Many studies have reported on childhood OSA treatments, such as continuous positive airway pressure, adenoidectomy, and different mandibular protrusion appliances.<sup>3</sup> However, the treatment effects were unclear. The twin-block appliance (TB) has often been used for maxillary protrusion for patients with retruded mandibles.<sup>4</sup> Other studies have also suggested TB as an airway expansion treatment.<sup>5</sup> Therefore, we examined that effects of the TB appliance on childhood OSAS.

## REPORT OF CASE

A 9-year-old boy (weight: 42.8 kg; height: 149.6 cm; body mass index: 19.1 kg/m<sup>2</sup>) was referred to the dental clinic at Ohu University Hospital. The chief complaint was maxillary protrusion. There was excessive overbite and labial tipping of the maxillary incisors. Cephalometric findings indicated maxillary protrusion associated with a posteriorly positioned mandible. The airway anteroposterior width was narrow.

The subject was instructed to use a wristwatch-type pulse oximeter (PULSOX-Me3000, Teijin, Japan) while in bed for 3 nights. The data were analyzed using the equipment's proprietary software (DS-Me, Minolta Co. Osaka Japan). We used the number of oxygen desaturations per hour (ODI) as an indicator of sleep-disordered breathing. The 2%, 3%, and 4% ODI scores represented the number of events per hour of recording time where blood oxygen levels decreased by 2%, 3%, or 4% or more. The sleep duration estimated by pulse oximetry was probably longer than the true total sleep time. In this case, the mean SpO<sub>2</sub> was 90%. Moreover, we measured SpO<sub>2</sub> and 2%, 3%, and 4% ODIs on 2 nights (**Table 1**). From these results, we

diagnosed the patient with skeletal II class malocclusion with a posteriorly positioned mandible and suspected childhood OSA.

This patient was treated with TB, an orthodontic functional appliance for protrusion of the mandible. We examined the craniofacial morphology, SpO<sub>2</sub>, and ODI at 3 time points (initial, start of TB treatment, and 6 months after TB treatment). In the cephalometric radiograph, the area of the oropharynx (area outlined by extension of palatal plane to posterior pharyngeal wall, posterior surface of soft palate, line parallel to palatal plane from tip of soft plate to dorsal surface of tongue, posterior inferior surface of tongue, line parallel to palatal plane through tip of epiglottis, and posterior pharyngeal wall) had increased, and the hypopharynx (the area outlined by inferior border of oropharynx, posterior surface of epiglottis, line parallel to palatal plane through point C4, and posterior pharyngeal wall) had decreased at the start of TB treatment. The 2%, 3%, and 4% ODI decreased at the start of treatment; however, the SpO<sub>2</sub> increased only at 6 months after treatment (**Table 1**).

From our results, 2% ODI immediately improved with TB treatment, but SpO<sub>2</sub> did not improve until 6 months later. In future, although nocturnal pulse oximetry may provide false positives, we will carefully examine the effect of TB treatment on skeletal and respiratory changes. The ODI changes in this study suggested that short-term TB treatment could improve childhood OSAS in those with posteriorly positioned mandibles.

**Table 1**—SpO<sub>2</sub> and ODI measurements in TB treatment by pulse oximeter.

	Initial	TB Treatment Start	6 Months after TB Treatment Start
SpO <sub>2</sub> (%)	90	92	96
2%ODI (times/h)	6.51	3.57	3.61
3%ODI (times/h)	2.89	2.51	1.27
4%ODI (times/h)	1.74	0.56	0.42

## CONCLUSION

TB was associated with improvement in skeletal and respiratory outcomes. There was a difference in the timing of the effects on ODI and SpO<sub>2</sub>. This suggested that long-term TB treatment was necessary to improve SpO<sub>2</sub>.

## REFERENCES

1. Nieminen P, Löppönen T, Tolonen U, Lanning P, Knip M, Löppönen H. Growth and biochemical markers of growth in children with snoring and obstructive sleep apnea. *Pediatrics* 2002;109:e55.
2. Zhong Z, Tang Z, Gao X, Zeng XL. A comparison study of upper airway among different skeletal craniofacial patterns in nonsnoring Chinese children. *Angle Orthod* 2010;80:267–74
3. Timothy F, Hoban MD. Obstructive sleep apnea in children. *Curr Treat Options Neurol* 2015;7:353–61.
4. Clark WJ. The twin block technique. A functional orthopedic appliance system. *Am J Orthod Dentofacial Orthop* 1988;93:1–18.

5. Zhang C, He H, Ngan P. Effects of twin block appliance on obstructive apnea in children: a preliminary study. *Sleep Breath* 2013;17:1309–14.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication January, 2016

Submitted in final revised form February, 2016

Accepted for publication February, 2016

Address correspondence to: Hisashi Hosoya, Assistant Professor, Ohu University, 31-1 Mitsumido, Tomita, Koriyama, Fukushima, 963-8041, Japan; Tel: +81-24-932-8931 (Ext.2345); Fax: +81-24-932-80714; Email Address: h-hosoya@den.ohu-u.ac.jp

## DISCLOSURE STATEMENT

This was not an industry supported study. The authors have indicated no financial conflicts of interest. The work was performed at the Ohu University School of Dentistry.

# A Pitfall of an Orthodontic Approach to Pubescent Obstructive Sleep Apnea: A Case Report

Keiko Maeda, PhD<sup>1,2,3,4</sup>; Eiki Itoh, PhD<sup>1,2,3,4</sup>; Yoko Okawara, DDS<sup>1</sup>; Yoichiro Takei, RPSGT<sup>2</sup>; Mina Kobayashi, PhD<sup>1,2,4</sup>; Yuichi Inoue, PhD<sup>1,2,3,4</sup>; Satoru Tsuiki, PhD<sup>1,2,3,4</sup>

<sup>1</sup>Japan Somnology Center, Institute of Neuropsychiatry, Tokyo, Japan; <sup>2</sup>Yoyogi Center for Sleep Disorders, Tokyo, Japan;

<sup>3</sup>Department of Somnology, Tokyo Medical University, Tokyo, Japan; <sup>4</sup>Foundation of Sleep and Health Sciences, Tokyo, Japan

Orthodontic treatment has potential as a fundamental approach in pubescent obstructive sleep apnea (OSA) patients with a small mandible. However, pitfalls of such treatment have not been documented. We report the case of a 15-year-old OSA patient (apnea hypopnea index [AHI] = 7.6 events/h) with a small mandible in whom we attempted to improve OSA by promoting the growth of the mandible with a mandibular advancement device. The AHI was reduced to 0.8 events/h with the device in place. However, neither notable growth of the mandible nor improvement of OSA without the device in place was observed after a 5-year follow-up (AHI = 7.8 events/h). It was retrospectively concluded that the optimal timing as an orthodontic treatment had already passed when the patient was introduced to our clinic. Hence, an orthodontic approach should be considered as soon as we encounter pubescent OSA so as not to lose an available window for definitive treatment.

**KEYWORDS:** obstructive sleep apnea, pubescent OSA, orthodontic treatment

**CITATION:** Maeda K, Itoh E, Okawara Y, Takei Y, Kobayashi M, Inoue Y, Tsuiki S. A pitfall of an orthodontic approach to pubescent obstructive sleep apnea: a case report. *Journal of Dental Sleep Medicine* 2016;3(2):73–74.

## INTRODUCTION

If the patient's predisposing factor for obstructive sleep apnea (OSA) is associated with a small mandible, the use of a mandibular advancement device (MAD) as an orthodontic approach is reasonable because nightly use of this device efficiently facilitates the growth of the mandible as long as patients are in the pubescent period, when mandibular growth can be expected in parallel with somatic growth.<sup>1–3</sup> Conversely, we recently experienced a case who was treated by an MAD but did not show either a fundamental improvement of OSA or growth of the mandible. This case highlights a potential pitfall of an orthodontic approach to pubescent OSA unless it is provided at a particular timing.

## REPORT OF CASE

A 15-year-old boy was diagnosed with mild OSA (apnea-hypopnea index [AHI] = 7.6 events/h), and was referred for oral appliance therapy using an MAD in our Sleep Apnea Dental Clinic. The patient had complained of frequent dozing off during school classes, chronic fatigue, and difficulty in waking up in the morning. His family reported loud snoring with episodes of apneas. His father was an untreated snorer who had experienced witnessed apneas. The score on the Japanese version of the Epworth Sleepiness Scale (JESS) at the patient's first visit was 13.<sup>4</sup> He had a thin physique with a BMI of 17.4 kg/m<sup>2</sup>. There was no hypertrophy of the tonsil or adenoidal tissue, and no chronic nasal obstruction.

The initial cephalogram revealed that, while the position of the maxilla was normal, the mandible showed both a small size and retroposition in comparison with the Japanese standard

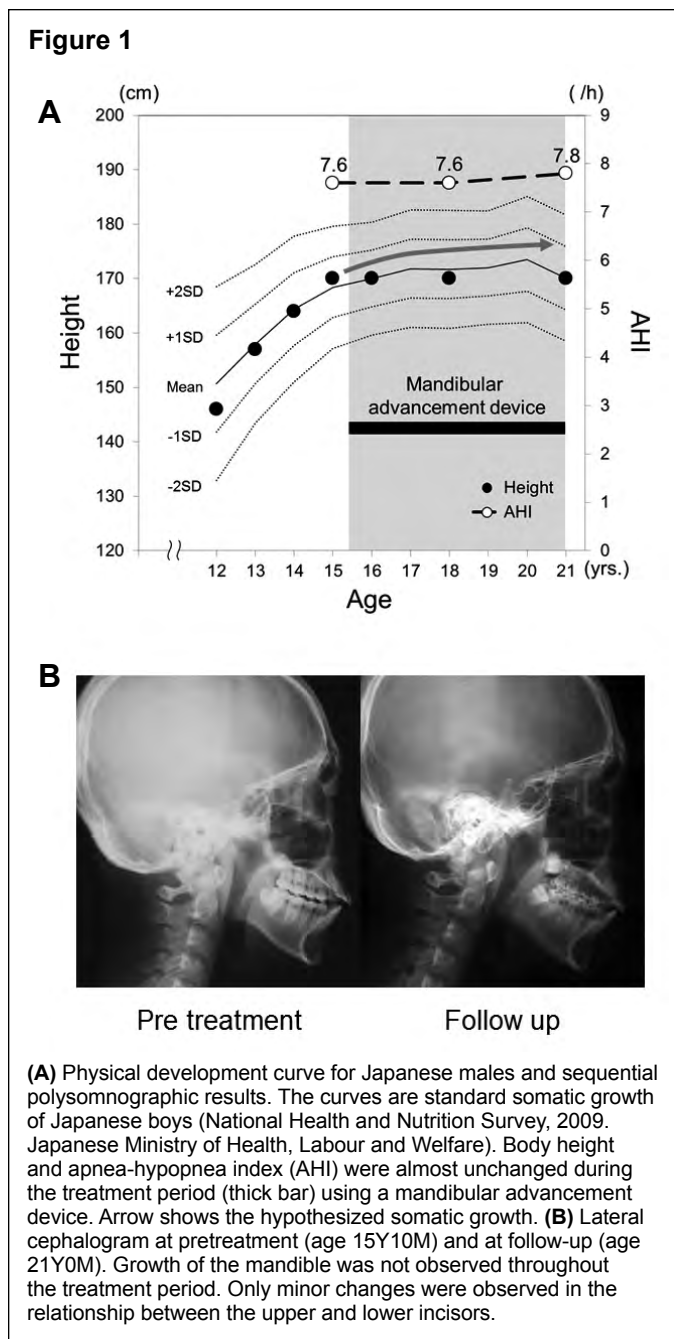
values (79.9° for the sella to nasion to subspinal point angle [SNA-- Japanese standard value = 81.4 ± 3.6°], 73.6° for the sella to nasion to supramental point [SNB; 79.6 ± 3.9°], and 6.3° for the subspinal point to nasion to supramental point angle [ANB; 1.8 ± 1.6°]).<sup>5,6</sup> According to the physical development curve for Japanese males, his physical growth spurt appeared to be close to being over (**Figure 1A**). However, we reasoned that the use of an MAD could induce residual growth of the mandible. After a full explanation of the details, including the possible effects of an MAD on mandibular growth and OSA, both the patient and his mother decided to use the device. Written informed consent was obtained from the patient's mother regarding the anonymous use of the patient's data for presentation and/or publication.

An adjustable two-piece type MAD was prescribed at an 8 mm ventrally advanced mandibular position. At 2 months after initiation of therapy, the patient became accustomed wearing his MAD for an average of 6 to 7 days/week. A sufficient improvement of AHI was observed with an MAD in place (AHI = 0.8 events/h) after 3 months, when the resolution of snoring and a reduction in daytime sleepiness were confirmed (JESS = 10). However, neither notable growth of the mandible by the 5-year-use of MAD (80.0° of SNA, 72.5° of SNB, and 7.7 of ANB) nor improvement of OSA without an MAD was observed after a 5-year follow-up (AHI = 7.8 events/h) (**Figure 1B**).

## DISCUSSION

Considering the good compliance with device usage in addition to the patient's cooperation with treatment, we retrospectively concluded that the optimal timing for MAD as an





orthodontic intervention had already passed when the patient was introduced to our clinic.

Although the concept of using an MAD for orthodontic treatment would be reasonable from the viewpoint of definitive therapy, there appear to be a few barriers that could weaken the feasibility of MAD therapy for a peripubertal OSA patient. First, as in our case, it is still clinically difficult to prospectively consider whether the mandible can really be anticipated to grow further in a pubescent patient, although the physical developmental curve serves as a good reference. Second, the above significant limitation and the knowledge of craniofacial growth/development are, to some extent, specific, and thus

unfamiliar to pediatric physicians as well as general dentists, unless they have specialized in sleep medicine.

This report, unlike the report of a similar pubescent OSA case who showed a favorable outcome with an MAD,<sup>1</sup> emphasizes the difficulty of MAD treatment as an orthodontic option for pubescent OSA. It is unlikely that this difficulty lies in the specific technique of dental treatment, and instead may be the result of a delayed diagnosis, due perhaps to limited recognition of the characteristic features of craniofacial growth/development. We propose that pediatric physicians and general dentists should consider an orthodontic approach as soon as they encounter pubescent patients with OSA to avoid losing the pertinent window for definitive treatment.

## REFERENCES

1. Ito S, Otake H, Tsuiki S, Miyao E, Noda A. Obstructive sleep apnea syndrome in a pubescent boy of short stature was improved with an orthodontic mandibular advancement oral appliance: a case report. *J Clin Sleep Med* 2015;11:75–6.
2. Maeda K, Tsuiki S, Nakata S, Suzuki K, Itoh E, Inoue Y. Craniofacial contribution to residual obstructive sleep apnea after adenotonsillectomy in children: a preliminary study. *J Clin Sleep Med* 2014;10:973–7.
3. Huynh NT, Desplats E, Almeida FR. Orthodontics treatments for managing obstructive sleep apnea syndrome in children: a systematic review and meta-analysis. *Sleep Med Rev* 2016;25:84–94.
4. Takegami M, Suzukamo Y, Wakita T, et al. Development of a Japanese version of the Epworth Sleepiness Scale (JESS) based on item response theory. *Sleep Med* 2009;10:556–65.
5. Nagaoka K, Kuwahara Y. Normal standards for various Roentgen cephalometric and cast model analyses in present day Japanese adults. Part 1. *Jpn Orthod Soc* 1993;52:467–80.
6. Sakamoto T, Miura F, Iizuka T. Linear Analyses on the developmental changes of dentofacial complex of Japanese by means of roentgenographic cephalometry. *J Stomatol Soc Jpn* 1963;30:169–82.

## ACKNOWLEDGMENTS

This work was performed at the Institute of Neuropsychiatry, Tokyo, Japan.

## SUBMISSION & CORRESPONDENCE INFORMATION

Submitted for publication February, 2016

Submitted in final revised form March, 2016

Accepted for publication March, 2016

Address correspondence to: Satoru Tsuiki, Institute of Neuropsychiatry, 1-21-10 Yoyogi, Shibuya-ku, Tokyo, Japan, 151-0033; Tel: +81-3-3374-9112

## DISCLOSURE STATEMENT

This was not an industry supported study. This study was supported by a Grant-in-Aid for Scientific Research (C) from the JSPS [# 25461180] to E. Itoh, by a Grant-in-Aid for Scientific Research (C) from the JSPS [#26463204] to Y. Okawara, by a Grant-in-Aid for Scientific Research (C) from the JSPS [#15K11463] to M. Kobayashi, by a Grant-in-Aid for Scientific Research (C) from the JSPS [#25515009] to Y. Inoue, by a Grant-in-Aid for Scientific Research (C) from the JSPS [#25515010 and 15H05301] to S. Tsuiki. The authors have indicated no financial conflicts of interest. The sponsors had no role in the design of the study, the collection and analysis of the data, or preparation of the manuscript.



## AADSM 2016 Educational Calendar of Events

AADSM Staff

*AADSM National Office, Darien, IL*

### **May 11**

Q&A Webinar: The Effect of Growth and Development on  
OSA in the Pediatric and Adolescent Population

### **June 9–11**

25<sup>th</sup> Anniversary Meeting  
Denver, CO

### **August 9–November 1**

Fall Study Club Program (live, web-based seminars)

### **September 17–18**

Essentials of Dental Sleep Medicine Course  
San Antonio, TX

### **November 5–6**

Advances in Dental Sleep Medicine Course  
Nashville, TN  
Essentials of Dental Sleep Medicine Course  
Nashville, TN

