

Cephalometric changes associated with MAD therapy

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Abstract

Study objectives: The main objectives of this study were to assess the effect of mandibular advancement device (MAD) therapy on the upper airway morphology, as well as the occurrence of dental and skeletal side effects following 1-year MAD therapy in patients with mild to moderate obstructive sleep apnea (OSA).

Methods: In this study we included 15 patients with mild to moderate OSA treated with MAD therapy. All subjects underwent sleep study and lateral cephalometric radiography at baseline and at 1-year follow-up. Lateral cephalograms were analyzed with respect to relevant variables.

Results: MAD therapy reduced apnea-hypopnea index (AHI) from 22.9 ± 5.9 to 9.7 ± 4.5 events/h ($P < 0.001$) after 1-year of therapy. Oral area enclosure (3697.0 ± 372.4 vs. 3381.5 ± 336.4 mm², $P < 0.001$), superior airway space width (8.9 ± 2.0 vs. 10.0 ± 2.0 mm², $P = 0.039$), soft palate width (10.9 ± 1.0 vs. 9.8 ± 1.4 , $P = 0.005$) and length (45.4 ± 3.8 vs. 43.9 ± 4.2 mm, $P = 0.033$) were significantly larger with the MAD intra-orally. Additionally, the tongue length decreased (84.1 ± 5.3 vs. 80.7 ± 5.9 mm, $P = 0.002$), while the tongue height increased significantly (27.0 ± 2.4 vs. 29.9 ± 2.5 mm, $P = 0.003$) with the MAD intra-orally. There were no significant changes in skeletal and dental cephalometric variables after 1 year of MAD therapy.

Conclusions: Our results show significant enlargement of the upper airway dimensions with the MAD intra-orally in patients with mild to moderate OSA. Although there were no significant changes in skeletal and dental cephalometric variables after 1 year of MAD therapy, close follow-up during MAD therapy is advisable to prevent potentially relevant occlusal changes.

Keywords: obstructive sleep apnea, mandibular advancement device, lateral cephalometry, side effects, upper airway

Introduction

Obstructive sleep apnea (OSA) is one of the most prevalent sleep-related breathing disorders characterized by repetitive episodes of pharyngeal collapse during sleep with associated airflow obstruction, intermittent hypoxemia, sympathetic excitation and sleep fragmentation.¹⁻³ OSA is recognized as a serious public health issue associated with the range of adverse cardiovascular events, such as hypertension, congestive heart failure, arterial fibrillation, stroke; increased risk for insulin resistance, type 2 diabetes and dyslipidemia,³⁻⁵ as well as the increased risk for excessive daytime sleepiness, impaired traffic safety, working ability and quality of life.^{3,4,6,7}

Treatment options for OSA patients include behavioral modification, weight reduction measures, positional therapy, upper airway surgery, continuous positive airway pressure (CPAP) and oral appliances (OA).^{2,8-12} Standard treatment with CPAP is highly efficacious for OSA patients but adherence to the treatment limits its overall effectiveness.^{1,2,13} OA treatment is a viable alternative in the treatment of OSA, especially in mild and moderate cases and in patients unwilling or unable to tolerate CPAP.¹⁰⁻¹² Many studies have shown significant decrease in AHI and normalization in oxygen desaturation index (ODI).^{4,9,12} In addition, there are studies showing that OA therapy improved glucose metabolism,^{4,14,15} as well as cognitive and psychomotor performances and quality of life in patients with mild to moderate OSA.^{16,17}

Mandibular advancement device (MAD) is the most commonly used OA which protrudes the mandible into forward and downward position therefore inducing anterior position of the tongue, soft palate, lateral pharyngeal walls, consequently improving airway patency.¹⁰⁻¹²

Lateral cephalometric radiographs have been extensively used in orthodontics to provide information about the sagittal and vertical relationships of the craniofacial skeleton, the soft tissue profile, the dentition, the pharynx morphology and the cervical vertebrae.^{18,19} The relationships among these structures are examined by linear and angular measurements and can be used for two-dimensional analysis of the upper airway and surrounding soft tissue structures in OSA patients, as well as for demonstration of occlusal changes following MAD therapy.¹⁹⁻²² Previous cephalometric studies have reported that cephalometric features such as longer maxilla, smaller overjet, shorter soft palate, longer mandibular plane to hyoid distance, facial height and reduced retropalatal airway space are associated with OSA.²²⁻²⁹ An inferiorly placed hyoid bone is one of the most consistent anatomical characteristics associated with OSA.^{24,26,28} Mostafiz et al. showed that MAD treatment increases oral cavity size by neutralizing an imbalance between soft tissue dimensions and surrounding bony structures.²⁵

Despite satisfactory efficacy of MAD therapy, it may develop subjective and objective side effects.^{9-11,30} Subjective side effects include temporomandibular joint (TMJ), myofascial or tooth pain, excessive salivation, dry mouth, gum irritation, morning stiffness and morning-after occlusal changes.³⁰⁻³² Most of the subjective side effects which are commonly reported in the initial period of MAD therapy are well tolerated and rarely lead to discontinuation of treatment.^{11,33,34}

Objective long-term side effects following MAD therapy in OSA patients have previously been described in terms of occlusal changes, including palatal inclination of the maxillary incisors, labial inclination of the mandibular incisors, slight mesial drift of the mandibular molars, and loss of contact between the posterior teeth or posterior open bite.^{11,30,34-38} Such changes were reported in 10 to 12% of OSA patients using MAD.³⁸

Although many studies have been published about the efficacy and side effects of MAD therapy, only few reported thorough analysis of the upper airway morphology and occlusal changes following long-term MAD therapy.

The objectives of this 1-year follow-up study were to assess:

1. The effect of MAD therapy on the upper airway morphology in patients with mild to moderate OSA.

1. The occurrence of dental and skeletal side effects following 1-year MAD therapy in patients with mild to moderate OSA.

Materials and methods

This study was approved by the Ethics Committee of the University of Split School of Medicine and all procedures were performed in accordance with the Declaration of Helsinki and its later amendments principles. Informed consent was obtained from all subjects included in this study prior to participation.

The baseline examinations included full-night attended polysomnography or polygraphy, physical examination and lateral cephalometric radiographs. Included subjects received custom-made adjustable MAD. The baseline examinations (sleep study and lateral cephalogram) were repeated at 1-year follow-up without and with the MAD intra-orally.

Subjects

Subjects with newly diagnosed mild to moderate OSA attending the Sleep Medicine Centre, University of Split School of Medicine were consecutively recruited in this study. Inclusion criteria were mild to moderate OSA, with an apnea-hypopnea index (AHI) greater than 5 events/h and lower than 30 events/h ($5 \leq \text{AHI} \leq 30$). A diagnosis of OSA was defined in accordance with the guidelines established by the American Academy of Sleep Medicine (AASM) and European Sleep Research Society (ESRS).^{1,2,8} Inclusion dental criteria for OA therapy of OSA were: at least 6 to 8 healthy teeth without movement in each jaw and mandibular advancement ability of at least 5 mm. Exclusion dental criteria were: known temporomandibular joint disorder and acute periodontal disease. Patients unable to understand the purpose of the study were also excluded.

Sleep assessment

The baseline diagnosis of OSA and 1-year follow-up assessment were performed by the same certified sleep physician with the same recordings on the same device at the time of follow-up with the MAD intra-orally to determine the MAD treatment efficacy.

Full-night in-laboratory polysomnography (Alice 5, PDX, Philips Respironics, Eindhoven, Netherlands) recordings included electroencephalography, electrooculography, mental and tibial electromyography, electrocardiography, nasal airflow, pulse oxymetry, thoracic and abdominal movements and snoring intensity, while full-night in-laboratory polygraphy (PolyMesam, MAP, Martinsried, Germany) included nasal flow, thermistor, pulse oxymetry, electrocardiography, thoracic and abdominal movements and snoring intensity.^{1,2,8} All data were stored on a personal computer and manually scored and evaluated in accordance with the published AASM and ESRs guidelines by the same certified sleep physician. The self-administrated questionnaire, the Epworth Sleepiness Scale (ESS), validated in Croatian language,³⁹ was used to measure excessive daytime sleepiness.

Mandibular advancement device

Patients who fulfilled inclusion criteria were supplied with the adjustable custom-made MAD (Silensor-sl, Erkodent, Pfalzgrafenweiler, Germany) for the treatment of OSA. Dental plaster models were formed based on alginate impressions of the upper and lower dental arches obtained by using an impression spoon. A silicon bite using George Gauge at maximum protrusion was registered for each subject. When initiating MAD treatment, the mandible

was set at 50% of the patient's maximum protrusion. Additional adjustment of the MAD was performed by the dental professional (T.G.) to allow further advancement of the mandible up to 75% of the maximum protrusion. The mean mandibular advancement with the MAD intra-orally was 68.8% of maximal protrusion, corresponding to 8.2 mm advancement. The adjustment of the protrusion was allowed until symptoms were adequately improved or until further mandibular advancement resulted in discomfort. The degree of mandibular protrusion and the vertical opening were kept constant during the follow-up period. All MADs were fabricated by the same dental technician and fitted and adjusted by the same dentist (T.G.).^{14,17}

Patients were instructed to use the appliance every night during sleep for as long as they could tolerate it. Each patient was given the personal sleep diary at the beginning of MAD therapy to monitor self-reported compliance. Patients were instructed to fill out the diary personally, on each day of the 1-year follow-up period, recording bedtime, wake-up time and the number of hours that the MAD was used. Patients with the adherence less than 4 hours on more than 70% of the days of the week were considered non-adherent to the MAD therapy.^{14,17}

Treatment was considered successful if AHI was <5 (complete responders), or if AHI reduction was $\geq 50\%$ (partial responders) from baseline which is considered to be clinically significant.^{9,40,41}

Table 1. Definitions of cephalometric measurements

Linear measurements	Definition	Angular measurements	Definition
Maxillary length	Cd-A	SNA	Angle from sella to nasion to subspinale
Mandibular length	Cd-Gn	SNB	Angle from sella to nasion to supramentale
Ramus height	Cd-Go	ANB	Angle from subspinal to nasion to supramentale
Corpus length	Go-Gn	Ramal plane angle	Po-Or-ramus tangent
Upper facial length	N-ANS	Mandibular plane angle	S-N-Me-Go
Lower facial height	ANS-Me	Upper incisor inclination angle	Uli-ANS-PNS
Anterior facial height	N-Me	Lower incisor inclination angle	Lli-MP
Vertical hyoid position	MP-H	Interincisal inclination angle	Uli-Lli
Overjet	The horizontal overlap of the maxillary and mandibular anterior teeth		
Overbite	The vertical overlap of the maxillary and mandibular anterior teeth		
Soft tissue measurements	Definition	Area measurements	Definition
Superior airway space	Narrowest width behind soft palate measured parallel to B-Go plane	Oral area enclosure	PNS-ANS-Go-Me
Middle airway space	Width through P measured parallel to B-Go plane		
Inferior airway space	Width base of tongue to posterior pharyngeal wall measured parallel to B-Go plane		
Tongue length	TT-Eb		
Tongue height	Maximum height perpendicular to TT-Eb		
Soft palate width	The width of soft palate		
Soft palate length	PNS-P		
Vertical airway length	PNS-Eb		

Lateral cephalometric radiographs

Lateral cephalometric radiographs were taken for each subject three times: at baseline, and after 1 year of MAD therapy, without and with the MAD intra-orally, using the standard techniques. The patients were standing in upright position, with the natural head posture tightly fixed by a cephalostat, the Frankfurt horizontal plane being parallel to the floor, and the teeth in full occlusion. They were instructed not to swallow and radiographs were taken with the patients exhaling slowly from a deep breath.^{20,27,29}

All cephalograms were taken by the same radiologic technologist in the Dental Radiology Center X-Dent, Split, Croatia, using Ortoceph OC200 D (Instrumentarium Dental, Tuusula, Finland). The exposure settings including effective radiation dose, the tube voltage and the tube current were as follows: 7.37 μ Sv, 85 kV and 13 mA with the exposure time of 10 seconds.

Lateral cephalograms were saved in JPEG image format on a personal computer and analyzed using the cephalometric software AudaxCeph (Audax, Ljubljana, Slovenia) with the integrated modified OSA SPLIT analysis and integrated calibration tool, which automatically calculated the distance between the selected points to the nearest tenth of a millimeter. Calibration of distances was performed prior to each tracing. The software allowed cursor-assisted tracking of anatomic landmarks for automatic calculation of distances, angles and areas. Cephalometric landmarks and variables used are presented in Table 1.^{19,24,25,29}

A, subspinale; ANS, anterior nasal spine; B, supra-mentale; Cd, condyilion; Eb, epiglottis base; Gn, gnathion; Go, gonion; H, hyoidale; Lli, lower incisor tip; Me, menton; MP, mandibular plane; N, nasion; P, soft palate tip; PNS, posterior nasal spine; Po, porion; S, sella; SN, sella-nasion distance; SNB; TT, tongue tip; Uli, upper incisor tip.

Oral area enclosure (OAE) was calculated as the region within the lines connecting posterior nasal spine (PNS), anterior nasal spine (ANS), gonion and menton²⁵ while vertical airway length (VAL) was calculated as the linear distance between PNS and the base of epiglottis (Eb).²⁴

All radiographs were analyzed by three investigators (F.M., I.G., T.G.) with an interval of at least one week between measurements and without knowledge of the respective results to accomplish reliability of measurements. The mean values of three measurements for each variable were used in the analyses.

Statistical analysis

Statistical analyses were performed using statistical software MedCalc for Windows, version 11.5.1.0 (MedCalc Software, Mariakerke, Belgium). The reproducibility of landmarks placement was assessed by the inter-class correlation coefficient (ICC) and the mean values for each variable of three observers were used in the analyses.

Continuous data were presented as mean \pm standard deviation. The Kolmogorov-Smirnov test was used to assess normality of data distribution. Comparisons of corresponding values at different time points of the study were performed using Wilcoxon matched pair test, as appropriate.

Spearman's rank correlation was used to explore associations between degree of mandibular advancement and AHI changes following MAD therapy. The statistical significance was set at $P < 0.05$.

Results

Baseline characteristics of patients and treatment efficacy

The study population consisted of 15 patients with mild to moderate OSA who were treated with MAD during the 1-year period. There were 14 male subjects and one female, mean age 51.2 \pm 8.9 years (range 32 to 65). Baseline characteristics of patients are shown in Table 2. Mean body mass index (BMI), neck and waist circumference did not change during the study period.

Table 2. Baseline characteristics of mild to moderate OSA patients

Parameters	Baseline
Age, years	51.2 \pm 8.9
Height, cm	180.0 \pm 7.2
Weight, kg	90.9 \pm 8.3
BMI, kg/m ²	28.1 \pm 2.7
Neck circumference, cm	42.0 \pm 2.2
Waist circumference, cm	99.9 \pm 7.0
ESS score	9.9 \pm 3.8
AHI, events/h	22.9 \pm 5.9
Mandibular advancement, mm	7.0 \pm 1.6
Mandibular advancement, %	68.8 \pm 5.1

Data are presented as mean \pm SD.

BMI, body mass index; ESS score, Epworth Sleepiness Scale score; AHI, apnea-hypopnea index.

The analyses of sleep recordings at baseline and after 1 year of MAD therapy are presented in Table 3.

Table 3. Excessive daytime sleepiness and sleep study data of mild to moderate OSA patients

Parameters	Baseline	1 year	P*
ESS score	9.9 \pm 3.8	6.0 \pm 2.8	<0.05
AHI, events/h	22.9 \pm 5.9	9.7 \pm 4.5	<0.001
Mean SpO ₂ , %	95.0 \pm 1.7	95.0 \pm 1.1	0.550
Minimum SpO ₂ , %	83.6 \pm 5.5	87.6 \pm 6.2	0.047
ODI, events/h	13.9 \pm 6.8	7.8 \pm 6.2	0.009
Snoring time, min	225.8 \pm 172.5	132.4 \pm 139.4	0.007

Data are presented as mean \pm SD.

ESS, Epworth Sleepiness Scale; AHI, apnea-hypopnea index; SpO₂, arterial oxygen saturation, ODI, oxygen desaturation index. *Wilcoxon matched pair test.

Overall, MAD therapy reduced AHI from 22.9 ± 5.9 to 9.7 ± 4.5 events/h, $P < 0.001$, after one year of therapy, with approximately 67% of patients achieving a clinically significant treatment success ($\geq 50\%$ AHI reduction). The mean mandibular advancement during 1-year period of MAD use was 68.8 % of the patient's maximum protrusion. There was a positive correlation between the degree of mandibular advancement and the changes in AHI ($r = 0.579$, 95% CI 0.042-0.857, $P = 0.038$). Overall subjective compliance based on sleep diaries was $81.3 \pm 10.7\%$ of days per week of MAD use during 1 year period. There were 13 regular users (87%) while two patients (13%) were considered non compliant after 1 year of MAD therapy.^{40,41}

Inter-observer reliability

Overall Interclass correlation coefficient (ICC) showed high degree of inter-reliability between the observers (ICC=0.995, 95% CI 0.989 - 0.999, $P < 0.001$).

Cephalometric measurements

Upper airway soft tissue cephalometric measurements

Cephalometric measurements of the upper airway soft tissues without the MAD and with the MAD intra-orally are presented in Table 4.

Table 4. Cephalometric soft tissue measurements of mild to moderate OSA patients without MAD and with MAD intra-orally

Parameters	Without MAD	With MAD	P*
Superior airway space width, mm	8.9 ± 2.4	10.0 ± 2.0	0.039
Middle airway space width, mm	6.8 ± 1.6	7.4 ± 1.6	0.454
Inferior airway space width, mm	8.6 ± 2.9	8.6 ± 1.8	0.939
Tongue length, mm	84.1 ± 5.3	80.7 ± 5.9	0.002
Tongue height, mm	27.0 ± 2.4	29.9 ± 2.5	0.003
Soft palate width, mm	10.9 ± 1.0	9.8 ± 1.4	0.005
Soft palate length, mm	45.4 ± 3.8	43.9 ± 4.2	0.033
Vertical airway length, mm	80.4 ± 5.7	79.4 ± 7.2	0.305
Oral area enclosure, mm ²	3381.5 ± 336.4	3697.0 ± 372.4	<0.001
Vertical hyoid position, mm	23.9 ± 6.4	19.3 ± 7.6	0.002

Data are presented as mean \pm standard deviation.
*Wilcoxon matched pair test.

OAE was significantly larger with the MAD intra-orally compared to the dimensions without the MAD (3697.0 ± 372.4 vs. 3381.5 ± 336.4 mm², $P < 0.001$). Additionally, soft palate width (SPW) and length (SPL) were significantly smaller with the MAD intra-orally, respectively, as well as the tongue length (TL) (84.1 ± 5.3 vs. 80.7 ± 5.9 , $P = 0.002$), while the tongue height (TH) increased significantly (27.0 ± 2.4 vs. 29.9 ± 2.5 mm, $P = 0.003$). Superior airway space width (SAS) was significantly larger with the MAD intra-orally, (8.9 ± 2.0 vs. 10.0 ± 2.0 mm², $P = 0.039$), as well. Middle (MAS) and inferior (IAS) airway space

dimensions did not change significantly with the MAD intra-orally. Individual OAE and SAS changes with the MAD intra-orally are shown in Figure 1.

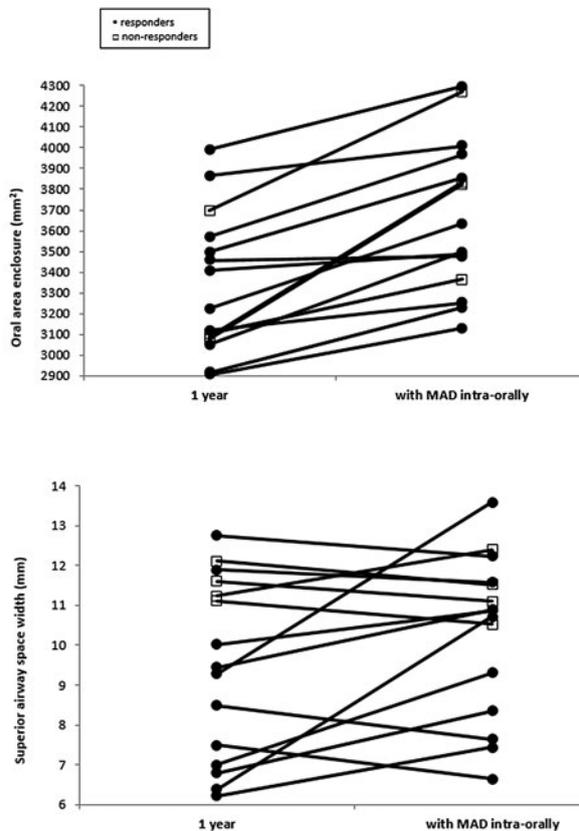


Figure 1. Individual oral area enclosure and superior airway space width changes with the MAD intra-orally. AHI-related responders are presented with filled circles and non-responders with empty squares.

Additionally to the upper airway soft tissue evaluation, mandibular plane to hyoid distance (MPH) decreased significantly with the MAD intra-orally (23.9 ± 6.4 vs. 19.3 ± 7.6 mm, $P = 0.002$).

Skeletal and dental cephalometric measurements

Results of cephalometric skeletal and dental evaluation at baseline and after 1 year of MAD therapy are presented in Table 5.

Table 5. Cephalometric skeletal and dental measurements of mild to moderate OSA patients at baseline and after 1 year of MAD therapy

Parameters	Baseline	1 year	P*
<i>Skeletal measurements</i>			
Maxillary length, mm	86.1 ± 4.6	84.9 ± 3.2	0.191
Mandibular length, mm	115.4 ± 5.8	113.9 ± 4.9	0.168
Ramus height, mm	58.4 ± 6.1	58.6 ± 3.9	0.946
Corpus length, mm	74.7 ± 5.4	74.5 ± 5.2	0.735
Upper facial height, mm	51.3 ± 3.2	51.8 ± 2.8	0.216

Parameters	Baseline	1 year	P*
Lower facial height, mm	72.4±4.4	72.3±4.6	0.542
Anterior facial height, mm	121.4±5.3	122.2±5.7	0.345
Vertical hyoid position, mm	23.8±6.5	23.9±6.4	0.685
SNA, °	81.6±2.5	80.9±3.1	0.167
SNB, °	77.7±3.6	77.0±3.5	0.133
ANB, °	4.7±1.7	4.1±2.2	0.216
Ramal plane angle, °	74.6±4.4	74.8±4.6	0.497
Mandibular plane angle, °	36.0±4.4	35.5±4.1	0.588
Occlusion plane angle, °	14.6±3.9	15.5±2.9	0.068
<i>Dental measurements</i>			
Upper incisor inclination angle, °	103.8±8.8	102.6±8.6	0.803
Lower incisor inclination angle, °	87.1±5.8	87.8±6.2	0.376
Inter-incisal inclination angle, °	139.7±9.8	141.2±10.5	0.191
Overjet, mm	3.5±0.6	3.1±0.8	0.080
Overbite, mm	2.2±1.8	2.0±1.8	0.414

Data are presented as mean±standard deviation.

SNA, sella-nasion-subspinale; SNB, sella-nasion-supramentale; ANB, subspinale-nasion-supramentale.

*Wilcoxon matched pair test.

There were no significant changes in skeletal cephalometric variables after 1 year of MAD therapy. The OJ changed between 2.4 and 5.3 mm, with the median value of 3.6 mm, while the OB changed between 0.1 and 6.4 mm, with the median value of 1.8 mm, although these changes were not significant. Upper incisors' inclination angle (Uli), lower incisors' inclination angle (Lli) and inter-incisal angle (Uli-Lli) did not change significantly after 1 year of MAD therapy (Table 5).

Discussion

The results of this study showed that the use of MAD with the mean mandibular advancement of 69% in mild to moderate OSA patients resulted in significant increase of the OAE and SAS, whereas no significant changes were seen in the MAS and IAS dimensions. Soft palate dimensions and TL decreased with the MAD intra-orally, while the TH increased significantly showing better distribution of soft tissues within the given oral cavity. Previous studies conducted among OSA patients during wakefulness showed similar results.⁴²⁻⁴⁵ Ryan et al. showed that the MAD placed intra-orally increased cross-sectional area of the upper airway, predominantly in the velopharynx and, to a lesser extent, in the oropharynx and hypopharynx.⁴⁵ The MAD has a direct effect on the velopharynx by increasing the antero-posterior dimension and may improve the patency of the upper airway in OSA patients.⁴²

Chan et al. showed that the increase in the total airway volume with the MAD intra-orally occurred predominantly because of an increase in the volume of the velopharynx and was mediated by an increase in its lateral dimensions

rather than antero-posterior airway dimensions.²³ Since we used two-dimensional cephalometric analysis in our study, measuring predominantly antero-posterior airway dimensions, smaller changes with the MAD intra-orally were expected. Additionally, MAD increases occlusal vertical dimension therefore producing the backward rotation of the mandible which might be another explanation why significant changes in MAS and IAS were not observed in this study.⁴⁴ If the mandible could be advanced in the direction perpendicular to the posterior pharyngeal wall without backward rotation, it would probably result in equally notable increases in the middle and inferior upper airway dimensions, as well.⁴⁴ Therefore, the increase in the occlusal vertical dimension of the OA should be minimized in order to maintain an enlarged upper airway size in OSA patients.

Hiyama et al. also showed significant increase in superior pharyngeal airway space by wearing the MAD while the sagittal dimensions of the middle and inferior pharyngeal airways did not change significantly,⁴⁴ which is similar as in our study. The significant change of the position of the hyoid bone in terms of smaller distance between the hyoid bone and the mandibular plane, has been shown while MAD intra-orally in this study. This may improve the morphology of the upper airway since the hyoid bone is closely connected to the cranial bones and the mandible through the suprahyoid muscles.^{23,46} Hyoid bone has no connection to other bones and is mobile therefore it can be shifted caudally by the extensive soft tissue within the maxillomandibular enclosure. Caudal displacement of the hyoid bone reflects upper airway anatomical imbalance in OSA patients.²⁶ The reduction of MPH in our study can be explained by the possibility that the mandibular advancement also pulled forward the muscles attached to the hyoid, consequently reducing the distance between the hyoid bone and the mandibular plane and improving the pharyngeal airway patency.^{23,46}

In addition to the morphological changes of the upper airway while MAD intra-orally, the results of the present study demonstrated the decrease of OJ and OB associated with the 1-year MAD therapy, although it was not statistically significant. It is generally hypothesized that these changes can be attributed to a labially directed force to the maxillary incisors during MAD therapy while the mandible attempts to return to a more dorsal position.^{33,36} In the study of Ghazal et al. a significant decrease in OB but not OJ was found,⁴⁷ while Ringquist et al. did not find similar significant changes after two years of OA therapy.³⁴

In our study skeletal cephalometric measurements did not change significantly following 1-year MAD therapy in mild to moderate OSA patients, while some authors showed slight decrease in SNA or SNB angle.^{30,37} It can be speculated that such changes might have been associated with the degree of mandibular advancement.

The relationship between degree of mandibular advancement and efficacy of an OA has previously been described.³⁶ The 67% of the maximum protrusion is widely used for the treatment of OSA patients and was recently demonstrated to be suitable to obtain the same effect as the maximum protruded position of the mandible in terms of antero-posterior dimension of the velopharynx.^{42,44} Therefore, we can assume there is no need of more extensive mandibular advancement considering treatment success and possible side effects. From the previous studies it

appears to be important to keep the mandibular advancement to a minimal efficient degree in order to minimize dental side effects.^{33,34} The positive correlation between degree of mandibular advancement and changes in AHI that has been shown in our study supports this observation.

Previously published data and our results indicate that skeletal and dental cephalometric changes might be associated with duration of MAD treatment rather than the degree of mandibular advancement.⁴⁸ Almeida et al. divided subjects using MAD into two groups based on duration of therapy, and they have found that most changes tended to develop and continue over time.³² Although these side effects may be substantial, we believe that the effective treatment of OSA supersedes the maintenance of baseline occlusion.

There are few limitations in our study. The sample size was relatively small therefore additional studies with larger number of subjects would be beneficial to contribute to the findings of this study. Assessment of possible side effects of MAD therapy in OSA patients over time involved repeated radiological examination therefore we did not include conventional control group in this study. Included subjects were acting as their own control subjects in this prospective cohort study with repeated measurements. Finally, there is a certain limitation in a two-dimensional evaluation using cephalometry compared to three-dimensional methods such as MRI or CBCT. Still, lateral cephalometry is widely used in clinical practice as a convenient and easy, low-cost and low radiation tool for evaluation of oral cavity and pharynx and it can identify craniofacial characteristics associated with OSA.²⁵

Conclusions

This study showed that the upper airway dimensions were enlarged significantly in patients with mild to moderate OSA with the MAD intra-orally. Moreover, no significant skeletal and dental cephalometric changes were observed, making MAD potentially beneficial and efficacious treatment modality for patients with mild to moderate OSA.

Implications for practice

Although MAD therapy may induce minor skeletal and occlusal changes, they are outweighed by benefits gained from using OA, especially considering the potentially life-threatening nature of OSA and its tendency to worsen over time. Patients with mild to moderate disease should not be left untreated and should not discontinue MAD therapy unless they are willing to adhere to another treatment modality.

Abbreviations:

AASM, American Academy of Sleep Medicine
 AHI, apnea/hypopnea index
 ANB, angle from subspinal to nasion to supramentale
 ANS, anterior nasal spine
 BMI, body mass index
 CBCT, cone beam computed tomography
 CPAP, continuous positive airway pressure
 Eb, base of epiglottis
 ESRS, European Sleep Research Society

ESS, Epworth Sleepiness Scale
 IAS, inferior airway space width
 ICC, inter-class correlation coefficient
 Lii, lower incisors' inclination angle
 MAD, mandibular advancement device
 MAS, middle airway space width
 MPH, mandibular plane to hyoid distance
 MRI, magnetic resonance imaging
 OA, oral appliance
 OAE, oral area enclosure
 OB, overbite
 ODI, oxygen desaturation index
 OJ, overjet
 OSA, obstructive sleep apnea
 PNS, posterior nasal spine
 SAS, superior airway space width
 SNA, angle from sella to nasion to subspinal
 SNB, angle from sella to nasion to supramentale
 SpO₂, arterial oxygen saturation
 SPL, soft palate length
 SPW, soft palate width
 STOP, Snoring, Tiredness, Observed Apnea, High Blood Pressure
 TH, tongue height
 TMJ, temporomandibular joint
 TL, tongue length
 Uii, upper incisors' inclination angle
 VAL, vertical airway length

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REFERENCES

1. Epstein LJ, Kristo D, Strollo PJ Jr, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. *J Clin Sleep Med*. 2009;5:263-276.
2. Bassetti C, Dogas Z, Peigneux P, eds. *Sleep Medicine Textbook*. Regensburg: European Sleep Research Society; 2014.
3. Jordan AS, McSharry DG, Malhorta A. Adult obstructive sleep apnoea. *Lancet*. 2014;383:736-747.
4. Phillips CL, Grunstein RR, Darendeliler MA, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea. *Am J Resp Crit Care Med*. 2013;187:879-887.
5. Bozic J, Galic T, Supe-Domic D, et al. Morning cortisol levels and glucose metabolism parameters in moderate and severe obstructive sleep apnea patients. *Endocrine*. 2016;53:730-739.
6. Quan SF, Chan CS, Dement WC, et al. The association between obstructive sleep apnea and neurocognitive

- performance-the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2011;34:303-314.
7. Bucks RS, Olaithe M, Eastwood P. Neurocognitive function in obstructive sleep apnoea: A meta-review. *Respirology*. 2013;18:61-70.
 8. Kushida CA, Nichols DA, Holmes TH, et al. Effects of continuous positive airway pressure on neurocognitive function in obstructive sleep apnea patients: the Apnea Positive Pressure Long-term Efficacy Study (APPLES). *Sleep*. 2012;35:1593-1602.
 9. Sutherland K, Vanderveken OM, Tsuda H, et al. Oral appliance treatment for obstructive sleep apnea: an update. *J Clin Sleep Med*. 2014;10:215-227.
 10. 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.
 11. Marklund M. Update on oral appliance therapy for OSA. *Curr Sleep Med Rep*. 2017;3:143-151.
 12. Marklund M. Long-term efficacy of an oral appliance in early treated patients with obstructive sleep apnea. *Sleep Breath*. 2016;20:689-694.
 13. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. *Sleep Med Rev*. 2011;15:343-356.
 14. Bozic J, Galic T, Supe-Domic D, et al. Morning cortisol levels and glucose metabolism parameters in moderate and severe obstructive sleep apnea patients. *Endocrine*. 2016;53:730-739.
 15. Anandam A, Patil M, Akinnusi M, Jaoude P, El-Solh AA. Cardiovascular mortality in obstructive sleep apnoea treated with continuous positive airway pressure or oral appliance: an observational study. *Respirology*. 2013;18:1184-1190.
 16. Naismith SL, Winter VR, Hickie IB, Cistulli PA. Effect of oral appliance therapy on neurobehavioral functioning in obstructive sleep apnea: a randomized controlled trial. *J Clin Sleep Med*. 2005;1:374-80.
 17. Galic T, Bozic J, Pecotic R, Ivkovic N, Valic M, Dogas Z. Improvement of Cognitive and Psychomotor Performance in Patients with Mild to Moderate Obstructive Sleep Apnea Treated with Mandibular Advancement Device: A Prospective 1-Year Study. *J Clin Sleep Med*. 2016;12:177-186.
 18. Poirrier AL, Fanielle J, Bruwier A, Chakar B, Poirrier R. Upper airway imaging in sleep-disordered breathing. *Acta Neurol Belg*. 2014;114:87-93.
 19. Denolf PL, Vanderveken OM, Marklund ME, Braem MJ. The status of cephalometry in the prediction of non-CPAP treatment outcome in obstructive sleep apnea patients. *Sleep Med Rev*. 2016;27:56-73.
 20. Muretić Ž, Lauc T, Ferreri S. Rendgenska kefalometrija. Zagreb: Školska knjiga; 2014. [In Croatian].
 21. Sutherland K, Deane SA, Chan AS, et al. Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea. *Sleep*. 2011;34:469-477.
 22. Sutherland K, Chan AS, Cistulli PA. Three-dimensional assessment of anatomical balance and oral appliance treatment outcome in obstructive sleep apnoea. *Sleep Breath*. 2016;20:903-910.
 23. Chan AS, Sutherland K, Schwab RJ, et al. The effect of mandibular advancement on upper airway structure in obstructive sleep apnoea. *Thorax*. 2010;65:726-732.
 24. Pae EK, Ferguson KA. Cephalometric characteristics of nonobese patients with severe OSA. *Angle Orthod*. 1999;69:408-412.
 25. Mostafiz W, Dalci O, Sutherland K, et al. Influence of oral and craniofacial dimensions on mandibular advancement splint treatment outcome in patients with obstructive sleep apnea. *Chest*. 2011;139:1331-1339.
 26. Tsuiji S, Isono S, Ishikawa T, Yamashiro Y, Tatsumi K, Nishino T. Anatomical balance of the upper airway and obstructive sleep apnea. *Anesthesiology*. 2008;108:1009-1015.
 27. Sforza E, Bacon W, Weiss T, Thibault A, Petiau C, Krieger J. Upper airway collapsibility and cephalometric variables in patients with obstructive sleep apnea. *Am J Respir Crit Care Med*. 2000;161:347-352.
 28. Genta PR, Schorr F, Eckert DJ, et al. Upper airway collapsibility is associated with obesity and hyoid position. *Sleep*. 2014;37:1673-1678.
 29. Vidović N, Mestrovic S, Dogas Z, et al. Craniofacial morphology of Croatian patients with obstructive sleep apnea. *Coll Antropol*. 2013;37:271-279.
 30. Fritsch KM, Iseli A, Russi EW, Bloch KE. Side effects of mandibular advancement devices for sleep apnea treatment. *Am J Respir Crit Care Med*. 2001;164:813-818.
 31. Martínez-Gomis J, Willaert E, Noguez L, Pascual M, Somoza M, Monasterio C. Five years of sleep apnea treatment with a mandibular advancement device. Side effects and technical complications. *Angle Orthod*. 2010;80:30-36.
 32. Almeida FR, Lowe AA, Sung JO, Tsuiji S, Otsuka R. Long-term sequelae of oral appliance therapy in obstructive sleep apnea patients: Part 1. Cephalometric analysis. *Am J Orthod Dentofacial Orthop*. 2006;129:195-204.
 33. Doff MH, Veldhuis SK, Hoekema A, et al. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on temporomandibular side effects. *Clin Oral Investig*. 2012;16:689-697.
 34. Ringqvist M, Walker-Engström ML, Tegelberg A, Ringqvist J. Dental and skeletal changes after 4 years of obstructive sleep apnea treatment with a mandibular advancement device: a prospective, randomized study. *Am J Orthod Dentofacial Orthop*. 2003;124:53-60.
 35. Pliska BT, Nam H, Chen H, Lowe AA, Almeida FR. Obstructive sleep apnea and mandibular advancement splints: occlusal effects and progression of changes associated with a decade of treatment. *J Clin Sleep Med*. 2014;10:1285-1291.
 36. Doff MH, Finnema KJ, Hoekema A, Wijkstra PJ, de Bont LG, Stegenga B. Long-term oral appliance therapy in obstructive sleep apnea syndrome: a controlled study on dental side effects. *Clin Oral Investig*. 2013;17:475-482.
 37. Doff MH, Hoekema A, Pruim GJ, Huddleston Slater JJ, Stegenga B. Long-term oral-appliance therapy in obstructive sleep apnea: a cephalometric study of craniofacial changes. *J Dent*. 2010;38:1010-1018.
 38. Almeida FR, Lowe AA, Sung JO, Tsuiji S, Otsuka R. Long-term sequelae of oral appliance therapy in obstructive sleep apnea patients: Part 1. Cephalometric analysis. *Am J Orthod Dentofacial Orthop*. 2006;129:195-204.
 39. Pecotic R, Dodig IP, Valic M, Ivkovic N, Dogas Z. The evaluation of the Croatian version of the Epworth sleepiness scale and STOP questionnaire as screening tools for obstructive sleep apnea syndrome. *Sleep Breath*. 2012;16:793-802.
 40. Tsuiji S, Kobayashi M, Namba K, et al. Optimal positive airway pressure predicts oral appliance response to a sleep apnoea. *Eur Respir J*. 2010;35:1098-1105.
 41. Vanderveken OM, Dieltjens M, Wouters K, De Backer W, Van de Heyning PH, Braem MJ. Objective measurement of compliance during oral appliance therapy for sleep-disordered breathing. *Thorax*. 2013;68:91-96.
 42. Tsuiji S, Hiyama S, Ono T, et al. Effects of a titratable oral appliance on supine airway size in awake non-apneic individuals. *Sleep*. 2001;24:554-560.
 43. Hiyama S, Ono T, Ishiwata Y, Kuroda T. Supine cephalometric study on sleep-related changes in upper-airway structures in normal subjects. *Sleep*. 2000;23:783-790.
 44. Hiyama S, Tsuiji S, Ono T, Kuroda T, Ohyama K. Effects of mandibular advancement on supine airway size in normal subjects during sleep. *Sleep*. 2003;26:440-445.
 45. Ryan CF, Love LL, Peat D, Fleetham JA, Lowe AA. Mandibular advancement oral appliance therapy for obstructive sleep apnoea: effect on awake/awake of the velopharynx. *Thorax*. 1999;54:972-977.
 46. Geoghegan F, Ahrens A, McGrath C, Hägg U. An evaluation of two different mandibular advancement devices on craniofacial characteristics and upper airway dimensions of Chinese adult obstructive sleep apnea patients. *Angle Orthod*. 2015;85:962-968.
 47. Ghazal A, Jonas JE, Rose EC. Dental side effects of mandibular advancement appliances – a 2-year follow-up. *J Orofac Orthop*. 2008;69:437-447.
 48. Hamoda MM, Kohzuka Y, Almeida FR. Oral appliances for the management of OSA: An updated review of the literature. *Chest*. 2017; doi: 10.1016/j.chest.2017.06.005. [Epub ahead of print].