The Effects of Mandibular Advancement Device on Pressure Pain Threshold of Masticatory Muscles: A Prospective Controlled Cohort Study

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Aims: To determine if pressure pain thresholds (PPTs) of masticatory and neck muscles change after the application of a mandibular advancement device (MAD) in patients with obstructive sleep apnea (OSA). **Methods:** A prospective study was conducted in a sample of 27 OSA patients (24 males and 3 females; mean age ± standard deviation [SD]: 54.8 ± 11.8, mean apnea-hypopnea index ± SD: 23.5 ± 13.3) and 27 age- and sex-matched healthy controls. Exclusion criteria were signs and symptoms of temporomandibular disorders (TMD), metabolic diseases, and use of antidepressants, analgesics, or anti-inflammatory drugs. A calibrated examiner evaluated PPTs of seven head and neck muscles bilaterally by using a Fischer algometer. In the OSA group, PPTs were recorded immediately before the MAD application (T_0), after 15 days (T_1), and after 6 months (T_2) of therapy; in the control group, PPTs were recorded at the same time intervals. PPT differences at baseline and over time within each group and between OSA and control groups were analyzed by Friedman and Mann-Whitney tests. **Results:** There were no PPT differences between groups at baseline. In the OSA group, PPTs of temporalis and masseter muscles decreased significantly at T_1 compared with T_0 ($P < .05$), but no differences were found at T_2. No significant PPT differences were found in the neck muscles or over time in the control group. **Conclusion:** MAD application induces a decrease of PPTs of masticatory muscles at the beginning of the therapy, but a physiologic adaptation occurs by 6 months.
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Keywords: *algometer, mandibular advancement device, masticatory muscles, obstructive sleep apnea, pressure pain threshold*

The prevalence of obstructive sleep apnea (OSA) syndrome is estimated to be 2% to 14% in community-screened patients.[1] This condition is associated with systemic hypertension, metabolic syndrome, heart failure, neurocognitive impairment,[2,3] and a significantly increased risk of mortality.[4,5] It can be treated effectively by behavioral therapy (eg, weight loss, controlling of sleeping position), continuous positive airway pressure (CPAP), surgical procedures, or the use of a mandibular advancement device (MAD).[6–8] MADs have been reported to be effective in the treatment of mild to moderate OSA and are recommended in patients who do not tolerate CPAP.[8]

Since OSA patients using a MAD must wear the device every night all life long, it is important to analyze the consequences of a forced mandibular advancement in order to know and be able to manage the commonly reported side effects, such as temporomandibular joint (TMJ) pain and sounds, myofascial pain, tooth pain, increased salivation or dry mouth, gum irritation, and morning-after occlusal changes.[9,10] The American Academy of Sleep Medicine guidelines indicate that the main reason for interrupting MAD therapy in patients is the development of temporomandibular disorders (TMD).[11]

The MAD forces the mandible in a forward and downward position that elongates the fibers of the jaw-elevator muscles and TMJ ligaments, which induces an increase of electromyographic (EMG) activity of masseter and temporalis muscles.[12–15] This in turn causes a strain on these muscles and on the retrodiscal tissues, which could cause

the onset of tenderness in the temporomandibular structures.[16,17] Some investigations have shown that OSA patients wearing a MAD are prone to develop TMD, TMJ discomfort, and muscle pain in the first period of therapy.[17–19] The development of muscle pain in patients wearing a MAD could be associated with an increased pain sensitivity of masticatory muscles, which can result in a decrease in muscle pressure pain threshold (PPT).[20] PPT is defined as the minimum pressure inducing pain and represents a reliable parameter to investigate variations in pain perception.[21,22] It can be reliably measured using an algometer,[23,24] which has been employed in many investigations evaluating masticatory and neck muscles both in TMD patients[25,26] and in healthy subjects.[22,27] Since recent studies have shown a correlation between masticatory muscle pain and neck muscle pain[28] and increased neck muscle activity during submaximal activation of masticatory muscles in the supine position,[29] a concomitant evaluation of masticatory and neck muscles is warranted.

Based on the null hypothesis that no changes would occur in PPTs of masticatory and neck muscles after a MAD application, the aim of the present study was to determine if PPTs of masticatory and neck muscles change after the application of a MAD in patients with OSA.

Materials and Methods

Sample Selection

A prospective controlled cohort study was conducted. A group of 47 consecutive patients with mild to moderate OSA (5/h < Apnea/Hypopnea index [AHI] < 30/h), who were referred by neurologists and otolaryngologists to the Department of Orthodontics of the University of Bologna for MAD therapy, was recruited. The OSA diagnosis was based on overnight polysomnography, scored manually according to standard criteria.[30] The control group was recruited by means of a leaflet campaign among the orderly staff of the Dental Department of the University of Bologna. All participants were informed about the study protocol procedures and signed an informed consent. Volunteers did not receive any monetary reward. The study protocol was approved by the local institutional review board.

Exclusion criteria were all conditions that can alter pain sensitivity such as metabolic and rheumatic diseases, consumption of antidepressants and membrane-stabilizing drugs during the last year, analgesic and anti-inflammatory drugs during the last month, pregnancy, menstrual and perimenstrual phase, tension-type headaches, malignancy, odontogenic pain, signs and symptoms of TMD, whiplash injury in the last 3 years,[31] periodontal disease, and the presence of less than six teeth per arch. The Italian version of the Epworth Sleepiness Scale (ESS)[32] was performed in the control group to exclude the presence of sleep disorders. The ESS is a self-administered questionnaire validated for use in OSA patients that is composed of eight questions that asks people to rate, on a 4-point scale (0 to 3), their usual chances of falling asleep. The total score is the sum of eight item scores and can range between 0 and 24. A recently proposed screening model found that the ESS has a high specificity (82.77%) and a moderate sensitivity (61.65%).[33] According to this model, males with an ESS score > 9 and females with an ESS score > 6 were excluded.[33]

In order to assess the exclusion criteria, an anamnestic questionnaire was administered to all patients and an orofacial pain specialist experienced in MAD management (I.M.) performed the clinical evaluations.

Among the 47 OSA patients examined, 27 (24 males and 3 females, mean age ± standard deviation [SD]: 54.8 ± 11.8, mean AHI ± SD: 23.5 ± 13.3) were eligible for the present study and were included in the OSA group; and 27 healthy age- and sex-matched volunteers (mean age ± SD: 53.3 ± 13.8) were enrolled in the control group.

Clinical Procedures

A dentist experienced in MAD management (M.L.B.) took alginate impressions (Hydrogum 5, Zhermack) of the dental arches. The George Gauge (Great Lakes Orthodontic Lab) was used to measure the maximum mandibular protrusion and to make a silicone interocclusal record (Occlufast Rock, Zhermack) for constructing the MAD; the amount of mandibular advancement was about 60% of the maximum protrusion. A dental technician manufactured dental plaster casts and fabricated the Silensor appliance for all the OSA patients. This MAD consisted of upper and lower acrylic bite plates connected by plastic straps running from the upper canine to the lower molar region bilaterally (Fig 1).

The same dentist fitted and adjusted the MADs to the OSA patients and instructed them to wear the device every night during sleep.

A calibrated examiner (F.B.) blind to the subject's group evaluated the PPTs of seven head and neck muscles bilaterally in all subjects of the OSA and control groups (Fig 2); these included the anterior, middle, and posterior bellies of the temporalis, masseter, sternocleidomastoid [SCM], splenius capitis, and occipitalis. In order to control for the presence or onset of muscle disturbances, the PPT of the hypothenar eminence was also assessed, since it is a point of muscle attachment not belonging to the masticatory system and is unlikely to be influenced by the therapy.

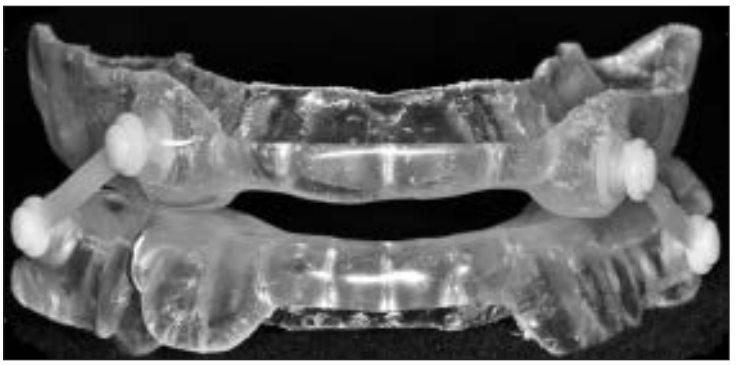

Fig 1 *(above)* Silensor appliance: Upper and lower acrylic bite plates connected by plastic straps running from the upper canine to the lower molar region bilaterally were fabricated to advance the mandible.

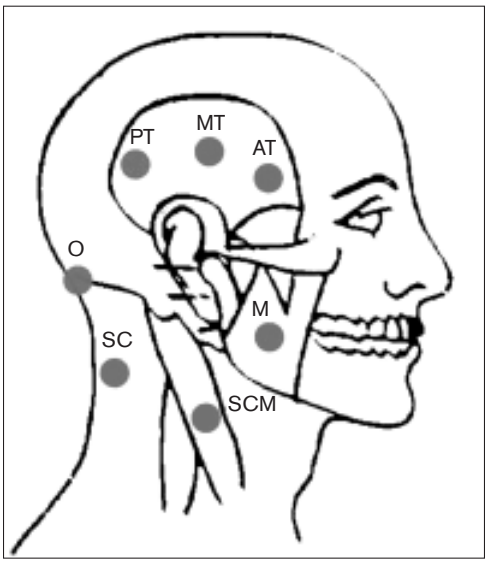

Fig 2 *(right)* Location of muscles evaluated (AT = anterior temporalis; MT = middle temporalis; PT = posterior temporalis; M = masseter; SCM = sternocleidomastoid; O = occipitalis; SC = splenius capitis).

PPTs were recorded by means of a Fischer algometer (Pain Diagnostics and Thermography), a force gauge fitted with a rubber disc with an area of 1 cm^2 which when pressed against a surface measures pressure in kg/cm^2 with a range up to 10 kg and 100-g divisions. Pressing the zeroing knob returns the indicator to zero after each measurement, but the force value obtained is held until it is pressed, allowing readings after removal of the algometer from the subject's body. The examiner trained for 1 week, learning to reach an increasing pressure rate of 100 g/sec continuously, as suggested by Fischer[21] and Jensen et al.[34] At the beginning of the first examination, the subjects were familiarized with the procedure by means of a demonstration on the left forearm and were instructed not to keep the teeth in contact to avoid contraction of the masticatory muscles during the measurements. The examiner performed the PPT recording of the SCM by holding the central part of the muscle with one hand and pressing the algometer with the other hand. During the examination session, the subjects were seated in an upright standardized position in a dental chair and were instructed to stop the examiner when they started to feel pain. The operator read off the value at that moment from the algometer and recorded the value as the PPT. Subjects were not informed of their PPT values and the examiner held the pressure indicator out of sight in order to avoid bias.

In the OSA group, PPTs were recorded immediately before the application of the MAD (T_0) and after 15 days (T_1) and after 6 months (T_2) of MAD therapy. In the control group, PPTs were recorded at the same time intervals. To ensure the relocation of the examined muscle sites during each session, two transparent pliable plastic templates were constructed for each subject, one for the head muscles and one for the neck muscles.

The reproducibility of the position of the templates was ensured by the following points of reference: tragus, eye external canthus, and external acromion apex of the clavicle. At each measurement session, three PPT recordings were performed for each muscle and the mean values were used for the statistical analysis.

At each time point, all subjects were asked about their compliance in wearing the MAD, about possible discomfort upon awakening, and asked, "did you feel pain in the cheeks and/or temples?" along with three follow-up questions: "if yes, was it spontaneous?"; "was it function related?"; and "did pain last more than one hour after the MAD removal?"

Statistical Analyses

A pilot study on the data collected from the first 12 consecutive OSA patients recruited was performed for the sample size calculation. Setting $\alpha = 0.05$ and $\beta = 0.20$, the effect size obtained was 0.59 and the requested sample size was 24 patients. The Shapiro-Wilk test denoted that PPT values were not normally distributed; therefore, median and interquartile range values were used to describe the data and nonparametric statistics were performed.

PPT values of right and left muscles were compared by using the Wilcoxon signed-rank test and since no statistically significant differences were detected, data from right and left muscles were merged for the statistical analysis. The Friedman test was performed to compare PPT values between time points within each group; post hoc analyses between T_1 and T_0 and between T_2 and T_0 were performed by means

Table 1 PPT at Different Time Points in OSA Group

Muscle	T_0 Median (IQR)	T_1 Median (IQR)	T_2 Median (IQR)	*P* value
Anterior temporalis	3.2 (2.6 to 3.9)	2.8 (2.2 to 3.4)**	3.1 (2.8 to 3.5)	.025*
Middle temporalis	3.4 (2.8 to 4.3)	2.9 (2.3 to 3.7)**	3.2 (2.8 to 4.0)	.001*
Posterior temporalis	4.3 (3.3 to 5.2)	3.5 (2.8 to 4.5)**	3.7 (3.3 to 4.9)	.001*
Masseter	2.6 (2.1 to 3.3)	2.4 (1.8 to 2.8)**	2.5 (2.3 to 3.2)	.012*
Sternocleidomastoid	1.9 (1.5 to 2.5)	1.8 (1.5 to 2.4)	1.9 (1.7 to 2.2)	.009*
Occipitalis	3.9 (3.2 to 4.7)	3.6 (2.8 to 4.5)	3.5 (3.1 to 4.7)	.091
Splenius capitis	2.8 (2.3 to 3.4)	2.6 (2.2 to 3.4)	2.8 (2.1 to 3.2)	.764
Hypothenar	7.4 (6.0 to 10.0)	7.5 (6.5 to 10.0)	7.4 (6.0 to 10.0)	.140

Friedman test. * = significant difference among time points; ** = significantly different from T_0 (post hoc analysis). OSA = obstructive sleep apnea; PPT = pressure pain threshold; IQR = interquartile range.

Table 2 PPT at Different Time Points in Control Group

Muscle	T_0 Median (IQR)	T_1 Median (IQR)	T_2 Median (IQR)	*P* value
Anterior temporalis	3.1 (2.6 to 3.7)	3.1 (2.8 to 3.7)	3.0 (2.8 to 3.6)	.171
Middle temporalis	3.5 (3.1 to 4.1)	3.6 (3.0 to 4.6)	3.5 (3.0 to 4.5)	.501
Posterior temporalis	4.0 (3.5 to 4.7)	4.0 (3.3 to 4.5)	4.0 (3.2 to 4.6)	.139
Masseter	2.5 (2.1 to 3.0)	2.5 (2.0 to 3.5)	2.6 (2.0 to 3.5)	.770
Sternocleidomastoid	1.6 (1.3 to 2.0)	1.7 (1.4 to 2.0)	1.8 (1.4 to 2.0)	.214
Occipitalis	3.5 (3.0 to 4.1)	3.5 (3.0 to 4.3)	3.5 (3.0 to 4.3)	.691
Splenius capitis	2.9 (2.3 to 3.5)	3.0 (2.2 to 3.7)	2.9 (2.2 to 3.7)	.338
Hypothenar	6.4 (5.6 to 10.0)	6.1 (5.8 to 10.0)	6.1 (5.8 to 10.0)	.597

Friedman test. PPT = pressure pain threshold; IQR = interquartile range.

of the Wilcoxon signed-rank test after applying the Bonferroni correction. The Mann-Whitney test was performed to compare PPT values at T_0 between the OSA and control groups and to compare the PPT differences at the time points between the two groups. For comparing the answers to the first question ("did you feel pain in the cheeks and/or temples?") between time points, a Cochran Q test was performed; post hoc analyses between T_1 and T_0 and between T_2 and T_0 were performed by means of the McNemar test after applying the Bonferroni correction. The McNemar test was performed in order to compare answers to the other questions between T_2 and T_1. An α level of .05 was set a priori. Statistical analysis was performed with IBM SPSS Statistics, version 20.0 (IBM Corp).

Results

The comparison of PPTs between groups at T_0 revealed no significant difference between the groups for all muscles, thus ensuring the comparability between groups.

Two withdrawals in the OSA group were registered between T_1 and T_2: the patients reported that they were unable to continue the therapy because of muscle pain in the masseter region caused by the MAD. The PPT recordings of these patients were excluded from the statistical analysis.

Significant differences were found between time points in the OSA group for the masseter, anterior, middle, and posterior temporalis, and SCM (Table 1); therefore, the null hypothesis was rejected. Post hoc analyses showed differences in PPTs between T_1 and T_0 for the anterior, middle, and posterior temporalis and masseter muscles (Table 1), but not for SCM, other neck muscles, or the hypothenar eminence. There were no differences between T_2 and T_0 for any muscle.

No significant differences were found in PPTs among time points in the control group (Table 2).

PPT differences between T_1 and T_0 were significant between the OSA and control groups for the anterior, middle, and posterior bellies of the temporalis and the masseter muscles (Table 3). No significant differences between the two groups in PPT values were found between T_2 and T_0 (Table 4).

Table 5 reports the outcomes of the questions: significant differences in pain occurrence were found between T_1 and T_0 (P = .02). At T_1, 13 patients reported pain in the cheeks and/or temples upon awakening, and for four of them the pain lasted more than 1 hour after the removal of the MAD in the morning: as previously reported, two of them abandoned the study between T_1 and T_2 and stopped wearing the MAD. At T_2, the number of patients who reported pain decreased to four and all of them reported function-related pain that lasted less than 1 hour.

Table 3 PPT Differences Between T_1 and T_0 in OSA and Control Groups

Muscle	T_1–T_0 OSA Median (IQR)	T_1–T_0 Control Median (IQR)	*P* value
Anterior temporalis	−0.3 (−0.7 to 0.2)	0.1 (−0.1 to 0.3)	.001*
Middle temporalis	−0.4 (−0.7 to 0.1)	0.0 (−0.1 to 0.3)	.001*
Posterior temporalis	−0.7 (−1.0 to −0.2)	0.0 (−0.2 to 0.2)	.001*
Masseter	−0.3 (−0.7 to 0.2)	0.0 (−0.1 to 0.2)	.005*
Sternocleidomastoid	0.0 (−0.4 to 0.2)	0.1 (−0.1 to 0.2)	.159
Occipitalis	−0.1 (−0.6 to 0.3)	0.0 (−0.2 to 0.2)	.077
Splenius capitis	−0.1 (−0.7 to 0.4)	0.0 (−0.2 to 0.2)	.348
Hypothenar	0.0 (−0.2 to 0.7)	0.0 (−0.1 to 0.2)	.118

Mann-Whitney test. * = statistically significant difference; PPT = pressure pain threshold; OSA = obstructive sleep apnea; IQR = interquartile range.

Table 4 PPT Differences Between T_2 and T_0 in OSA and Control Groups

Muscle	T_2–T_0 OSA Median (IQR)	T_2–T_0 Control Median (IQR)	*P* value
Anterior temporalis	0.1 (−0.1 to 0.4)	0.1 (−0.2 to 0.3)	.964
Middle temporalis	0.0 (−0.2 to 0.2)	0.1 (−0.1 to 0.3)	.333
Posterior temporalis	0.0 (−0.3 to 0.2)	0.1 (−0.1 to 0.3)	.390
Masseter	0.1 (−0.1 to 0.3)	0.0 (−0.1 to 0.3)	.780
Sternocleidomastoid	0.1 (−0.1 to 0.2)	0.1 (−0.2 to 0.2)	.703
Occipitalis	0.0 (−0.2 to 0.5)	0.0 (−0.2 to 0.3)	.893
Splenius capitis	0.0 (−0.1 to 0.2)	0.0 (−0.2 to 0.2)	.469
Hypothenar	0.0 (0.0 to 0.4)	0.0 (−0.1 to 0.3)	.465

Mann-Whitney test. PPT = pressure pain threshold; OSA = obstructive sleep apnea; IQR = interquartile range.

Table 5 Comparison of Answers to Questions in OSA Group at Different Time Points

	T_0 (n = 27) n (%)	T_1 (n = 27) n (%)	T_2 (n = 25) n (%)	*P* value
Pain in the cheeks and/or temples	0 (0)	13 (48)**	4 (16)	.001*
Spontaneous pain	–	3 (11)	0 (0)	.250
Function-related pain	–	13 (48)	4 (16)	.004*
Pain lasting more than 1 hour	–	4 (15)	0 (0)	.125

Cochran and McNemar tests. * = statistically significant difference; ** = significantly different from T_0. OSA = obstructive sleep apnea.

Discussion

The present study has shown that after the application of the MAD, there was a significant modification over time in the PPTs of masticatory muscles. Post hoc analyses showed a significant decrease in PPTs of the temporalis and masseter muscles at T_1, but by 6 months of therapy these PPT values had returned to baseline levels. These results can be explained by the immediate stretching induced by the MAD that produces a forced elongation of muscle fibers that physiologically tend to recover the original muscle length by increasing their activity.[35] The data obtained at T_2 indicate a physiologic adaptation of the tissues to the stress induced by the MAD.

The inclusion of the control group of healthy subjects matched for age and sex added quality to the experimental protocol; the analysis showed that in the healthy subjects PPTs were constant over time, thus confirming a role of the MAD in the PPT decrease. Moreover, the control group allowed a further analysis that compared group differences in PPT values between time points and confirmed a significant decrease of PPTs of the masseter and temporalis muscles 15 days after the MAD application, thus strengthening the results. No significant group differences occurred in PPTs in the OSA group between T_2 and T_0. These results confirm that after the initial PPT decrease, there was an adaptation of the muscles by 6 months of therapy.

Recent findings have shown a neuromuscular interaction between jaw and neck muscle activity during submaximal clenching specifically in the supine position[29,36] and a correlation between masticatory muscle pain and neck muscle pain in TMD patients.[28] Therefore, the present study also assessed PPTs of neck muscles. The PPTs of the SCM muscle showed a significant change between time points but post hoc analyses did not show significant differences between any time points. This suggests that the MAD therapy does not markedly influence PPTs of the SCM muscle. These results are supported by those of Giannakopoulos et al, who showed a low level of contraction activity of neck muscles during voluntary activation of masticatory muscles.[29,36] On the basis of the present results, it can be postulated that this moderate increase of activity cannot lead to an increase in muscle pain sensitivity. No significant differences in PPTs of the other neck muscles were found between time points in the OSA group or between the groups. This may be due to the MAD producing protruding force concentrated on the masseter and temporalis muscles.

The present findings are supported by previous studies showing that an elongation of muscle fibers leads to fatigue that not only compromises function but also increases pain sensitivity,[16,17,37,38] and so account for the muscle pain reported in the literature after the start of a MAD therapy.[17–19] Moreover, an investigation conducted in an animal model showed that chronic sagittal advancement of the lower jaw induces

a muscle adaptation during the early period specifically by transformation of fast, fatigue-prone fibers to slower, fatigue-resistant fibers, and by an increase in size of the capillary bed, which augmented the regional blood flow.[39] These processes could be related to the initial decrease of PPTs of masticatory muscles after the start of the MAD therapy and the later adaptation found in the present study.

In the present investigation, about half of the patients reported cheek and/or temple pain upon awakening at T_1 and in the majority of patients who reported pain upon awakening, this pain was function-related and lasted less than 1 hour. Of three patients who reported spontaneous pain, two withdrew from the study and stopped the MAD therapy between T_1 and T_2 because of pain in the masseter region. The number of patients who reported pain at T_2 decreased to four and all four of these patients reported function-related pain that lasted less than 1 hour. The trend in PPT changes in the present investigation can explain these findings, indicating that a physiologic adaptation may have occurred after an initial increase of muscle sensitivity. However, more research is needed to analyze more time points during MAD therapy to clarify exactly when PPT adaptation may occur and if it is stable over time.

Previous studies of mandibular protruding appliances that investigated the changes in electromyographic (EMG) activity of masticatory muscles have reported different outcomes; some found that the EMG activity of masticatory muscles increases[12–15] while others showed decreased EMG activity of the lateral pterygoid, masseter, and anterior digastric muscles during the therapy.[40,41] Nevertheless, these studies are very heterogenous and include animal models and both adolescent and adult subjects wearing different protruding devices for different purposes (eg, skeletal modifications, OSA treatment). Therefore, the outcomes provided are not completely comparable, and a clear conclusion on the effect of a MAD application on masticatory muscle EMG activity cannot be reached. It would have been interesting to correlate the variation in PPTs with EMG data and the lack of EMG recordings in the present protocol may represent a weakness. There are also other limitations that include the patients being treated only with an advancement of 60% of maximum mandibular protrusion; further studies comparing PPTs of masticatory muscles at different mandibular advancements would be useful for elucidating the relationship between the magnitude of the mandibular advancement and the change in PPTs over time. In addition, the control subjects were diagnosed as not having OSA on the basis of an accurate anamnesis and ESS, and not by means of a specific diagnostic examination for OSA, such as polysomnography. Moreover, even if the presence of a control group adds validity to the outcomes, the ideal study design should have included a placebo group wearing an appliance not producing any mandibular advancement. A strength of the study design was the inclusion of an examination of the PPTs of the hypothenar eminence, a point of muscle attachment on the palm of the hand above the base of the little finger; since it does not belong to the masticatory system, it cannot be directly influenced by the therapy and so was used to control for the presence or onset of muscle disturbances.

Proper management of orofacial disorders that may develop or become symptomatic after application of a MAD can lead to good patient compliance and the best outcomes.[11,42] Development of pain may be linked to a modification of muscle activation thresholds, and the extent of that modification could depend on the immediacy and size of the jaw advancement. Orofacial pain specialists experienced in the overall care of oral health, dental occlusion, and the TMJ should manage and control MAD therapy[42] in such a way as to adapt the progression of jaw advancement to the needs of individual patients and to prevent and manage possible side effects.

Conclusions

The present study has shown that at the beginning of MAD therapy, the PPTs of temporalis and masseter muscles in OSA patients significantly decreased but returned to baseline values after 6 months.

Acknowledgments

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