Effect of Experimental Tooth Clenching on the Release of β-Endorphin

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Aims: To investigate the association between experimental tooth clenching and the release of β-endorphin in patients with myofascial temporomandibular disorders (M-TMD) and healthy subjects. **Methods:** Fifteen M-TMD patients and 15 healthy subjects were included and assigned an experimental tooth-clenching task. Venous blood was collected and pain intensity was noted on a visual analog scale. The masseter pressure pain threshold (PPT) was assessed 2 hours before the clenching task and immediately after. A mixed-model analysis of variance was used for statistical analyses. **Results:** Significant main effects for time and group were observed for pain intensity and PPT, with significantly lower mean values of pain intensity ($P < .001$) and PPT ($P < .01$) after the clenching task compared with baseline. M-TMD patients had significantly higher pain intensity ($P < .001$) and significantly lower PPT ($P < .05$) than healthy subjects. No significant time or group effects were observed for the level of β-endorphin. Neither pain intensity nor PPT correlated significantly with β-endorphin levels. **Conclusion:** This experimental tooth-clenching task was not associated with significant alterations in β-endorphin levels over time, but with mechanical hyperalgesia and low to moderate levels of pain in healthy subjects and M-TMD patients, respectively. More research is required to understand the role of the β-endorphinergic system in the etiology of M-TMD. *J Oral Facial Pain Headache 2014;28:159–164. doi: 10.11607/ofph.1210*

Key words: *beta-endorphin, bruxism, masseter muscle, temporomandibular joint disorders*

Intense muscle exercise can induce analgesia by activating the endogenous opioid system and other pain inhibitory mechanisms.[1] β-endorphin levels increase in response to muscle exercise[2] and are involved in biologic reward and motivational systems.[3] β-endorphin may also account for mood changes (sensations of pleasantness and euphoria) that may occur after muscle exercise.[4]

β-endorphin is a neuropeptide and is synthesized from the precursor pro-opiomelanocortin, predominately in the pituitary, but also in the hypothalamus.[1] Stressors, such as psychological stress and painful stimuli, can activate the hypothalamus and pituitary to release β-endorphin into the central nervous system (CNS)[5] and the circulatory system,[6] respectively. Elevation of β-endorphin levels in the CNS is associated with analgesia.[7] β-endorphin exerts its analgesic effect by targeting μ-receptors in the peripheral nervous system and CNS,[1,8] and may play a role in impaired endogenous pain inhibition, which has been reported in patients with temporomandibular disorders (TMD),[9] fibromyalgia,[10] and whiplash-associated disorders.[11]

Bruxism is a repetitive jaw muscle activity characterized by clenching or grinding of the teeth and can occur during wakefulness or sleep.[12] Self-reported awake bruxism has a prevalence of approximately 20%,[13,14] and sleep bruxism has a prevalence of 8%.[15] One possible consequence of bruxism is chronic pain in the masticatory muscles, that is, myofascial TMD (M-TMD),[16] but only a fraction of bruxers develop M-TMD. Furthermore, it has been observed that the severity of M-TMD is not associated with the degree of bruxism,[17] and it seems that bruxism is not a predictor of M-TMD.[18,19]

Table 1 Clinical Characteristics of the Study Sample

	M-TMD patients (n = 15)	Controls (n = 15)	*P*	Test
Age, y; mean ± SD	31.8 ± 13.4	31.6 ± 12.4	.966	Independent Samples *t* test
Duration of M-TMD, mo; mean ± SD	58.6 ± 60.3	0.0 ± 0.0	<.001	Mann-Whitney *U* test
No. of muscle sites with pain on palpation, max 20; median (interquartile range)	14 (8)	2 (2)	<.001	Mann-Whitney *U* test
No. of TMJ sites with pain on palpation, max 4; median (interquartile range)	1 (1)	0 (0)	<.001	Mann-Whitney *U* test
Self-reported awake bruxism	11	3		
Self-reported sleep bruxism	11	7		
Blood sampling at 8 am	8	8		
Blood sampling at 1 pm	7	7		

TMJ, temporomandibular joint.

Several etiologic factors have been suggested for tooth grinding and clenching,[20] but the exact mechanism is not known. One biologic explanation might be that tooth clenching activates the reward system in a similar manner as observed in other types of muscle exercises, ie, that repetitive concentric contractions of healthy jaw muscles normally lead to a release of β-endorphin and thus cause antinociception, while in M-TMD patients, the β-endorphin system is impaired and contributes to the perception of pain. Therefore, the aim of this study was to investigate the association between experimental tooth clenching and the release of β-endorphin in patients with M-TMD and healthy subjects. The following hypotheses were tested: *(1)* patients with M-TMD have a significantly lower β-endorphin level than healthy subjects; *(2)* the level of β-endorphin in plasma is significantly increased in response to experimental tooth clenching in healthy subjects, but not in patients with M-TMD; and *(3)* β-endorphin levels in plasma are negatively correlated with pain levels and pressure pain thresholds (PPTs) in both groups.

Materials and Methods

Subjects

Table 1 presents the clinical characteristics of the study sample. Fifteen patients (11 females and 4 males) with M-TMD (mean age ± SD: 31.8 ± 13.4 years) and an age- and sex-matched control group consisting of 11 females and 4 males (mean age ± SD: 31.6 ± 12.4 years) participated in this study. The M-TMD patients and the control group were part of another study, which consisted of a comprehensive data collection.[21,22] All patients were recruited among consecutive patients referred to the Department of Orofacial Pain and Jaw Function, Faculty of Odontology, Malmö University, Malmö, Sweden, and were diagnosed with M-TMD after a clinical examination.[23] The control group was recruited from Malmö University. One author (AD) examined the patients to confirm a diagnosis of M-TMD and to confirm that the control group was healthy. The M-TMD patients and the control subjects were questioned about awareness of awake and sleep bruxism.

The inclusion criteria for the M-TMD group were *(1)* age > 18 years, *(2)* a diagnosis of M-TMD pain,[23] *(3)* moderate or more severe pain in the masseter muscles upon palpation at the clinical examination and on the experimental day, and *(4)* continuous or persistent pain in the jaw muscles for more than 6 months.

Inclusion criteria for the healthy controls were *(1)* age > 18 years, *(2)* healthy, and *(3)* no orofacial pain complaints.

Exclusion criteria for both groups were conditions that can influence the pain sensitivity, such as *(1)* systemic inflammatory connective tissue diseases (eg, rheumatoid arthritis), *(2)* whiplash-associated disorders, *(3)* chronic widespread muscle pain conditions (eg, fibromyalgia), *(4)* neuropathic pain or neurologic disorders (eg, oromandibular dystonia), *(5)* pain of dental origin, *(6)* pregnancy or lactation, *(7)* high blood pressure, and *(8)* ongoing dental treatment. Medications that could interfere with the blood sampling or the pain sensitivity were excluded, such as *(9)* anticoagulants and *(10)* analgesics 1 week before the experiment (eg, paracetamol, nonsteroidal anti-inflammatory drugs [NSAIDs], salicylate drugs, and opioids), or other medications that would influence pain perception (eg, antidepressants or antiepileptic drugs). Patients with factors that could affect the experimental tooth clenching, such as *(11)* extensive restorations (eg, full fixed or removable dentures) and *(12)* severe skeletal malocclusions, were also excluded. Exclusion criteria were assessed in each subject by collecting their medical history.

This experiment was conducted at the Department of Orofacial Pain and Jaw Function at Malmö University. The Helsinki Declaration guidelines were followed, and the Regional Ethics Review Board at

Lund University approved the study (2010/31). Before participation, subjects signed an informed-consent form and were informed that they could refrain from the study at any time without any consequences. After completion of participation, subjects were financially compensated.

Study Design

This case-control study consisted of one 4-hour session scheduled at 8 am or 1 pm, in which the subjects performed a repetitive tooth-clenching task at 50% of maximal voluntary contraction force (MVCF). Table 1 presents the number of subjects who had blood sampling at 8 am and at 1 pm. At the beginning of the session, a venous blood sample was collected for further analysis of β-endorphin, and baseline assessments of MVCF, pain intensity, and PPT were made. A 120-minute relaxation period followed, after which the subjects performed the clenching task. A second venous blood sample was drawn, and pain intensity and PPT were then assessed.

Throughout the trial, subjects sat upright in a dental chair with a head support. One operator (AD) made all assessments.

Experimental Tooth Clenching

A bite-force transducer (Aalborg University, Denmark) placed between the molars on the right side was used to assess MVCF (kg). Three times, the subjects were asked to bite down on the transducer and were verbally encouraged to clench as intensely as possible for 2 to 3 seconds. Mean MVCF was calculated from the three registrations. During the 20-minute experimental tooth clenching, subjects carried out 20 bouts of clenching at 50% of their mean MVCF. Each bout lasted 30 seconds, with 30-second intervals between bouts. This model was chosen since in healthy subjects it evokes low pain levels, which were similar to the baseline values of the M-TMD patients.[24] The bite-force transducer displayed clenching force, and subjects were instructed to maintain 50% mean MVCF by continuously watching the display.

Blood Sampling

Venous blood samples were collected in 3-mL EDTA Vacutainers (Becton, Dickinson, and Company; Franklin Lake, NJ, USA). Directly after withdrawal, the samples were centrifuged (2,000 g, +20˚C) for 10 minutes, and the plasma was transferred into Eppendorf tubes and stored at –70˚C until analysis.

Assessment of PPT

An electronic algometer (Somedic Sales AB) was used to assess PPT, defined as the amount of pressure (kPa) needed to produce the slightest sensation of pain. A 1-cm^2 probe was applied to the attachment of the right masseter muscle with a constant pressure of 30 kPa/s. The mean of three measurements made at 60-second intervals was calculated. Acceptable reliability was previously found for PPT measured on the masseter muscle.[25]

Assessment of Pain Intensity

A 100-mm visual analog scale (VAS) was used to assess pain intensity (anchor definitions: no pain and worst imaginable pain).

Analysis of β-Endorphin

On the day of analysis, the plasma samples were thawed and subjected to solid phase extraction using SPE-C18E columns (Phoenix Pharmaceuticals Inc). The eluates were lyophilized and reconstituted in assay buffer before analysis of β-endorphin by using the commercially available Endorphin Beta (Human) Immunoassay kit (Phoenix Pharmaceuticals Inc) according to the manufacturer's instructions.

Statistical Analyses

All statistical analyses were done in the Statistical Package for the Social Sciences for Windows, version 20 (SPSS, IBM). Analyses were performed two-tailed at a significance level of 5%. All variables are expressed as means and SDs unless otherwise stated. The Shapiro-Wilk's test was used to test the data for normality. MVCF and pain intensity were normally distributed, while PPT and β-endorphin levels were normalized after Ln-transformation (natural logarithm). Parametric statistics were used for all statistical analyses except for categorical variables, as well as for M-TMD duration, since this variable was not normally distributed.

The Mann-Whitney *U* test was used to determine significant differences between groups for duration of M-TMD (months) and number of muscle and temporomandibular joint (TMJ) sites with pain on palpation.

Independent samples *t* tests were used to investigate significant differences in age and MVCF between groups. A mixed-model analysis of variance (ANOVA) was used to test for significant main effects of time and group, and for interaction effects between time and group on pain intensity, PPT, and β-endorphin level. Spearman's correlation test adjusted for multiple testing with Bonferroni correction was used to test for significant correlations between pain intensity, PPT, and β-endorphin level at rest and following contraction in each group.

A sample size calculation was made, based on the mean ± SD of the plasma level of β-endorphin in healthy subjects,[26] 56 ± 18.3 pg/mL, using $\beta = .80$ and $\beta = .05$. It was found that 11 subjects in each group would be sufficient to detect a difference of 1 SD in mean β-endorphin level.

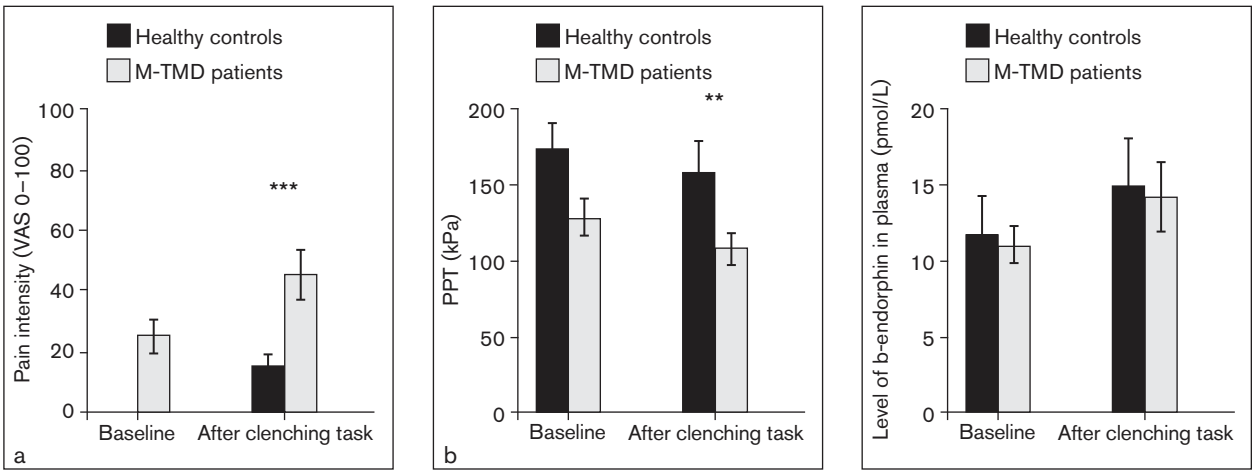

Fig 1 **(a)** Pain intensity (0–100 VAS) and **(b)** PPT (kPa) measured at baseline and after experimental tooth clenching in 15 M-TMD patients and 15 healthy subjects. Significant change compared with baseline for both groups (healthy controls and M-TMD patients), $^{**}P < .01$, $^{***}P < .001$. A significant difference between M-TMD patients and healthy subjects was observed for pain intensity ($P < .001$) and for PPT ($P < .05$).

Fig 2 β-endorphin levels in plasma (pmol/L) measured in 15 patients with M-TMD and 15 healthy subjects, at baseline and after an experimental clenching task. No significant alterations were observed.

Results

MVCF

M-TMD patients had a significantly lower MVCF than healthy subjects ($P < .05$; 42.5 kg and 56.6 kg, respectively).

Pain Intensity

Main effects for time and group were observed for pain intensity ($P < .001$), but no interaction effect was detected ($P > .05$). Mean pain intensity increased significantly after experimental tooth clenching compared with baseline, and M-TMD patients had significantly higher pain intensity than healthy subjects (Fig 1a).

PPT

Significant main effects for time ($P < .01$) and group ($P < .05$) were observed for PPT, but there was no interaction effect ($P > .05$). PPT was significantly lower after experimental tooth clenching compared with baseline, and M-TMD patients had a significantly lower PPT than healthy subjects (Fig 1b).

β-Endorphin in Plasma

β-endorphin levels in plasma were unaltered over time ($P = .38$), and no significant differences were observed between groups ($P = .69$) (Fig 2). No interaction effects between time and group were observed ($P = .31$). A significant difference was not observed ($P = .15$) between the level of β-endorphin in the plasma collected in the morning (am) and in the plasma collected in the afternoon session (pm).

Correlations

A significant negative correlation was observed between pain intensity and PPT after experimental tooth clenching for M-TMD patients ($P < .01$); that is, high pain intensity was associated with a low PPT. No other significant correlations were observed between β-endorphin level, pain intensity, and PPT in the M-TMD patients or the healthy subjects.

Discussion

The main findings of this study were that *(1)* a significant difference between M-TMD patients and healthy subjects was not observed for the level of β-endorphin in plasma, *(2)* experimental tooth clenching did not increase β-endorphin levels, and *(3)* β-endorphin in plasma did not correlate significantly with pain intensity or PPT in any group, but *(4)* a significant negative correlation was observed between pain intensity and PPT for M-TMD patients.

Chronic pain conditions (eg, fibromyalgia and whiplash-associated disorder) exhibit impaired endogenous pain inhibition.[10,11] It was expected that the M-TMD patients would have significantly lower levels of β-endorphin than healthy subjects at baseline, but no significant differences were observed, which agrees with another study.[27] It seems that patients with regional chronic pain, such as the participating M-TMD patients, do not exhibit significantly reduced levels of β-endorphin, while patients with more widespread pain have impaired endogenous pain inhibition that could be associated with reduced levels of

β-endorphin. In contrast, one study observed that patients with limited jaw opening and movement-evoked pain in the TMJ had significantly higher levels of β-endorphin than healthy subjects.[28] The higher pain intensities exhibited by the patients in that study compared to the M-TMD patients in the present study might explain these ambiguous results. Furthermore, since β-endorphin levels were unaltered in both groups, the significantly higher pain intensities and significantly lower PPTs observed in the M-TMD patients at baseline and after the clenching task compared with healthy subjects were not caused by an impaired β-endorphin system. A peripheral release of algesic substances, however, might explain this.[29]

β-endorphin levels in plasma are generally increased after muscle exercise.[2] The present results indicate that a repetitive experimental tooth-clenching task was not associated with such release of β-endorphin in M-TMD patients or healthy subjects. Muscle exercise that is dynamic, of long duration, and shifts the muscles into anaerobic metabolism is more likely to increase β-endorphin levels than short, static, aerobic muscle exercise.[2,30] The M-TMD patients and healthy subjects performed 20 bouts of clenching at 50% of MVCF during 20 minutes, and this model was insufficient to alter the level of β-endorphin. It is possible that another experimental tooth-clenching model, such as clenching until exhaustion, would have yielded different results. It must also be emphasized that the experimental tooth-clenching model used in the present study does not necessarily represent tooth clenching per se, and therefore the results should be interpreted with caution. This experimental tooth-clenching model was chosen because this model evokes low levels of pain in healthy subjects, similar to baseline values reported by the M-TMD patients. Most likely, tooth clenching occurs in patients at lower intensities for longer time periods, since tooth clenching at 100% of MVCF only can be maintained for a few seconds.[31,32] Thus, it cannot be excluded that a tooth-clenching task with high external validity might cause a shift toward anaerobic metabolism and induce a release of β-endorphin, mitigate pain, and shift the participant's mood into a euphoric condition.

It could also be considered whether the status of bruxism in the M-TMD patients and the healthy controls could have affected the outcome of the β-endorphin levels. However, it has been demonstrated that regular exercise does not seem to influence the levels of β-endorphin.[33] In addition to this, no differences in the resting values have been observed for the level of β-endorphin in exercise-trained and nontrained subjects.[34] Therefore, it is not likely that the status of bruxism in the study sample affected the results.

To the authors' knowledge, this is the first study to investigate the relationship between β-endorphin levels in M-TMD patients and healthy subjects in response to experimental tooth clenching. The low levels of pain that were evoked in the healthy subjects were similar to the M-TMD patients' self-reported baseline values, which is a strength of this study. Furthermore, the healthy control group had no prior experience of orofacial pain and was matched according to age and sex with the M-TMD patients. All participants were asked about awareness of awake and sleep bruxism, which is a positive feature of the study. A limitation of the study is that blood sampling was not conducted at the same time points during the day in all subjects (blood was collected either in the morning session or the afternoon session), since the β-endorphin levels vary throughout the day.[24] However, the results imply that the time of blood collection did not influence the β-endorphin levels in the study. The study sample was small but was in accordance with the power analysis. A larger study sample might have yielded different results on the influence of tooth clenching on β-endorphin levels.

In conclusion, this repetitive experimental tooth-clenching model was not associated with an increase of circulating β-endorphin in M-TMD patients or in healthy subjects, nor was there a significant difference in β-endorphin levels observed between M-TMD patients and healthy subjects. No significant correlation was observed between β-endorphin level, pain intensity, and PPT in any group. Moderate and low levels of pain were evoked in M-TMD patients and healthy subjects, respectively, by the clenching exercise. It seems that the higher levels of pain in the M-TMD patients were not caused by impaired β-endorphin release. Further studies are warranted to elucidate the role of β-endorphin in the etiology of M-TMD.

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