Tooth Clenching Until Exhaustion Evokes Exercise-Induced Hypoalgesia in Healthy Persons and in Patients with Temporomandibular Disorders

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Aims: To investigate whether static jaw clenching can activate endogenous pain modulation and to compare the magnitude between healthy individuals and patients with temporomandibular disorder (TMD) myalgia. **Methods:** Thirty-three healthy volunteers (17 women and 16 men) and 20 women with TMD myalgia participated. Exercise-induced hypoalgesia (EIH) was examined by recording pressure pain thresholds (PPTs) in the masseter (MA) and brachioradialis (BR) muscles during tooth clenching until exhaustion. Pain and fatigue were assessed before and after clenching, and pain amplification was examined by applying a painful mechanical pressure at the MA for 2 minutes while assessing pain every 30 seconds. Analyses of data included repeated measures analysis of variance. **Results:** In the contracting MA, PPTs increased over time in all three groups ($P < .001$), while PPTs in the relaxed BR increased only in the men ($P = .045$). Pain intensity and fatigue in the MA increased after contraction in all groups ($P < .003$) and was higher in the women with TMD than in the healthy women ($P < .001$). Only the women with TMD showed pain amplification ($P < .001$). **Conclusion:** Tooth clenching until exhaustion could activate EIH locally; ie, the magnitude of EIH in the MA was similar in women with TMD myalgia and pain-free women, indicating no deficient EIH in women with TMD. However, only women with TMD showed pain amplification during application of continuous painful pressure. *J Oral Facial Pain Headache 2019;33:14–24. doi: 10.11607/ofph.2011*

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Myalgia that is manifested in temporomandibular disorders (TMD) is the most frequent chronic pain condition in the orofacial area. TMD myalgia afflicts 5% to 12% of the population and is twice as prevalent in women as in men.[1] As in other chronic myalgic conditions, pain, tenderness, and functional limitations—such as reduced jaw opening and chewing difficulties—are the most common symptoms.

Current knowledge suggests that chronic TMD pain is caused by a combination of pain amplification and dysfunctional pain inhibition.[2] Pain amplification may occur due to peripheral and central sensitization mechanisms, such as temporal summation. While this is a normal phenomenon, studies have shown that sex differences occur in temporal summation of pain (with higher magnitudes in women[3]) and that TMD patients show increased pain responses to temporal summation.[4]

Endogenous pain modulatory systems play an important role in pain perception: Without inhibition of pain, a painful stimulus would not stay local and bearable.[5] Endogenous pain inhibition may be experimentally activated by several methods, including conditioned pain modulation (CPM) and exercise. Both aerobic exercise and static muscle contractions have been shown to elevate muscle pressure pain thresholds (PPTs) in healthy individuals.[6–8]

Healthy women seem to have less efficient pain inhibition than men.[9] Furthermore, several studies have shown dysfunctional CPM in various chronic pain conditions, including TMD.[5,10–12] Some studies have also shown dysfunctional exercise-induced hypoalgesia (EIH) in fibromyalgia, whiplash-associated disorder (WAD), and localized shoulder myalgia.[13–16] In most conditions, deficient pain inhibition is seen both locally

and at remote sites, suggesting that this is a generalized deficiency even if the pain is localized.[5,14]

To the authors' knowledge, no previous studies have explored whether static contraction of jaw-closing muscles (ie, tooth clenching) can activate EIH or whether there are sex differences in EIH in healthy subjects, nor has any study investigated EIH in chronic TMD myalgia patients. The present study therefore aimed to test the following hypotheses: *(1)* Tooth clenching until exhaustion activates endogenous pain inhibition both locally (ie, contracting muscle) and remotely (ie, distant relaxing muscle) in healthy, pain-free volunteers; *(2)* The magnitude of EIH is similar in healthy men and women, since hypoalgesia can be regarded as a normal response to exercise; *(3)* Patients with chronic TMD myalgia show dysfunctional EIH both locally and remotely during static contraction until exhaustion of the painful jaw muscles, but not during static contraction of a pain-free, nontrigeminal muscle; and *(4)* A constant painful mechanical pressure leads to pain amplification in TMD myalgia patients but not in healthy, pain-free volunteers.

Materials and Methods

Participants

Healthy, age-matched male and female volunteers recruited via advertisement and active recruitment were included. Inclusion criteria were age 18 to 40 years of age and free of pain with good general health. Female patients with chronic TMD myalgia pain who were age matched to the healthy female volunteers were recruited from the public dental health school in Stockholm, Sweden, and Karolinska Institutet, Huddinge, Sweden, via advertisement and active chairside enrollment. The inclusion criteria were 18 to 40 years of age and a diagnosis of myalgia according to the Diagnostic Criteria for TMD (DC/TMD)[1]; ie, characteristic pain intensity (CPI)[1] during the last month > 30/100 and a pain duration > 6 months.

Exclusion criteria for all participants were: a diagnosis of fibromyalgia, WAD, or systemic inflammatory disorders (eg, rheumatoid arthritis, psoriatic arthritis); severe psychiatric disorders; neuropathic pain; pain of dental origin; high blood pressure; pregnancy or lactation; and use of analgesic drugs such as acetaminophen and nonsteroidal analgesic drugs (NSAIDs) 24 hours prior to the experiment.

Ethical approval from the Regional Ethical Review Board in Stockholm was obtained prior to the study start (2013/629-31/4). All participants were informed about the study, and oral and written consents were obtained. The study was performed in accordance with the Helsinki declaration.

A previous study that included 21 healthy controls, 20 women with shoulder myalgia, and 20 women with fibromyalgia obtained significant differences in PPT changes between groups during static contraction of the quadriceps and infraspinatus muscle.[14] An earlier study obtained significant differences with only 14 women with fibromyalgia and 14 healthy controls.[13] Thus, it was estimated that 15 to 20 participants would be sufficient in the present study. A power calculation showed that 20 subjects in each group would be needed to obtain a clinically significant group difference of 30% (standard deviation [SD] 20%) with a power of 99% at a significance level of 5%.

Procedure

Before the experiment, the healthy participants completed a health questionnaire and the DC/TMD Symptom Questionnaire included in the DC/TMD Axis II to ensure that they did not fulfill a TMD pain diagnosis. The TMD myalgia patients completed a health questionnaire and the full DC/TMD Axis II questionnaire included in the DC/TMD classification.[1] From the DC/TMD questionnaire, CPI and functional limitation (based on their scores on the Graded Chronic Pain Scale [GCPS]) were retrieved, as well as their levels of depression (Patient History Questionnaire-9 [PHQ-9]), anxiety (Generalized Anxiety Disorder-7 [GAD-7]), and somatization (Patient History Questionnaire-15 [PHQ-15]).

The participants were comfortably seated in a conventional dental chair with the head, neck, and back supported to minimize unwanted movement.

A schematic drawing of the procedure is shown in Fig 1. The procedure used was a modified version of that presented previously.[14] The experiment started with baseline recordings of PPT and maximum voluntary force (MVF) for bite and grip force. Two experiments then followed: In the first, the participants' pain amplification was tested, and in the second, EIH was tested. Pain intensity was assessed during both experiments, and the second experiment also included assessment of fatigue. The whole session lasted approximately 2 hours.

The sides used for the experiments were randomized in an alternating order, and the two experiments were always performed on opposite sides (ie, if the right side was used for assessment of pain amplification, the left side was used for assessment of EIH).

Assessment of Pain Intensity and Fatigue

The patients' CPI (the mean of the current pain intensity and the average and worst pain intensities during the last month, assessed with a 0 to 10 numeric rating scale and then multiplied by 10) was assessed before the experiment and used for patient description. For baseline assessments of pain intensity and for pain

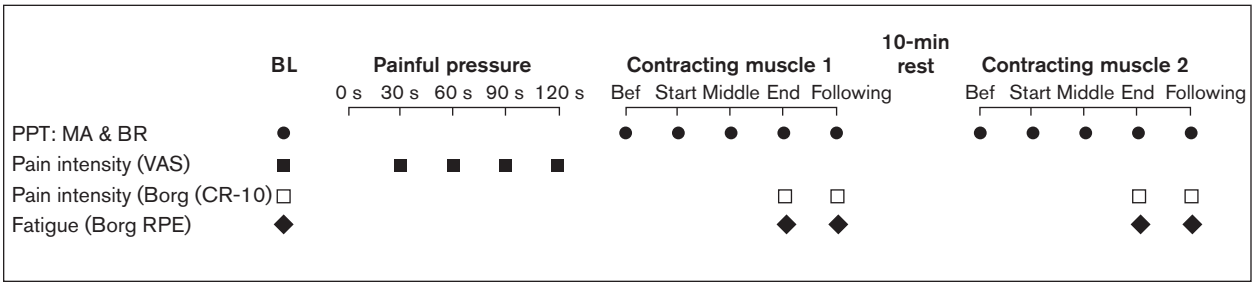

Fig 1 Schematic drawing of the experimental protocol. Baseline (BL): maximum voluntary force (MVF) and pressure pain threshold (PPT) were recorded, and pain intensity (Borg's CR-10 scale), and fatigue (Borg's RPE scale) assessed in the masseter (MA) and brachioradialis (BR) muscles unilaterally. A painful pressure was then applied to the MA, and pain intensity was assessed with a visual analog scale (VAS) every 30 seconds. Baseline PPT recordings were then done over either the MA or BR (before [Bef]), after which the participants performed a submaximal clenching task (tooth or fist; 25% of MVF) for as long as they could endure or a maximum of 5 minutes. During clenching, PPTs were recorded at the beginning of clenching (start), mid-time (middle), end (end), and 10 minutes after contraction (following). Pain and fatigue were assessed directly after and 5 minutes after contractions. After a 10-minute rest, the participant performed submaximal contraction of the other muscle in a similar manner.

intensity during static muscle contraction, Borg's category rating (CR-10) scale was used.[17] This is a combined numeric and verbal scale that ranges from 0 (nothing at all) to 10 (extremely strong). For assessment of pain during the pain amplification experiment, a 0- to 100-mm visual analog scale (VAS) was used with the end points 0 (no pain) and 100 (maximal imaginable pain). Perceived fatigue/exertion was assessed with Borg's Rating of Perceived Exertion (RPE) scale,[18] which ranges from 6 (no exertion at all) to 20 (maximal exertion). Both Borg scales have been validated and are reliable.[19,20]

Assessment of PPTs

PPTs were recorded at the masseter (MA) and brachioradialis (BR) muscles on either the right or left side in the healthy participants (alternating order) and on the most painful side in the patients (on the left side in 12 patients and on the right side in 8). An electronic pressure algometer (Somedic AB) was used with a chosen pressure increase rate of 50 kPa/second. The sites for PPT assessment were identified and marked on the skin overlying the muscle with a felt pen. The chosen site for the MA was the central, most prominent part of the muscle, approximately 2 cm above its insertion at the angle of the mandible. For the BR, the length from the lateral epicondyle of the humerus to the head of the ulna was first measured, and a point in the center of the muscle (in the medial-lateral direction) corresponding to the proximal one-third of this measurement was chosen.

The participants were instructed to press a button exactly at the moment when the PPT was reached; ie, when the sensation transformed from pressure to pain. Baseline PPTs were recorded three times, and the mean of the three recordings was used. Single assessments of PPT were used at all other time points.

Recording of Maximum Voluntary Force

MVF was recorded on the same side as the PPT recordings. A bite-force transducer (Aalborg University) was used for assessment of bite force. This device consists of a bite fork and force transducer with a digital display for visual feedback of the clenching force. The bite fork was placed between the molars on the chosen side. For assessment of grip force, a grip force meter (Force Gauge MAP 80K1, Kern & Sohn) was used that also had a digital display for visual feedback. During contraction, the armrest of the dental chair supported the contracting arm and elbow.

The participants performed three maximal isometric contractions for 5 seconds each, with 1 minute of rest in between contractions. The mean of the three recordings was calculated and used as the MVF. From this value, 25% of the individual MVF was calculated.

Pain Amplification

During this experiment, a suprathreshold (ie, painful) pressure stimulus was continuously applied with the algometer at one of the resting MAs. The pressure was determined by first recording the pressure that the subject rated as corresponding to 4/10 on the CR-10 scale, and then the pressure corresponding to 7/10.[21] The mean pressure of these two values, corresponding to about 5/10 on the CR-10 scale, was calculated and used as a painful stimulus. The stimulus was applied for 2 minutes, and every 30 seconds the participant was asked to rate the pain intensity.

Exercise-Induced Hypoalgesia

To activate local EIH in the orofacial region, the participants performed a submaximal isometric contraction of the MA (ie, tooth clenching), during which PPTs were recorded at the contracting MA and at the relaxed BR on the same side. To activate local EIH

in an extratrigeminal (nonpainful) region, participants performed a submaximal isometric contraction of the BR (clenching of the fist), while PPTs were recorded at the contracting BR and at the relaxed MA on the same side in a similar manner. The BR was used as a control muscle because it is easily accessible. The contraction force of each muscle corresponded to 25% of its individual MVF.

The experiment started with assessments of PPTs at both muscles before clenching. The participants then began the clenching. The clenching levels were continuously visualized on a display for feedback. The participants were encouraged to keep the same force level during the entire experiment, which continued until exhaustion or for a maximum of 5 minutes. During this time, PPTs were assessed every 30 seconds over both muscles in the same order starting 25 seconds after the beginning of the clenching. During tooth clenching, PPTs were assessed first at the contracting MA and then at the ipsilateral resting BA muscle. During clenching of the fist, PPTs were assessed first at the contracting BR and then at the ipsilateral resting MA. Finally, PPTs were recorded again 10 minutes after the experiment. After a subsequent 10-minute rest period, the experiment was repeated with contractions of the other muscle. The order of the contractions was randomized in a balanced way; ie, half of the subjects started with contractions of the MA and half of them started with contractions of the BR.

PPTs were analyzed before, at the start, middle, end, and following contractions for each individual:

- Before = PPT assessed in the resting muscle just before start of contractions
- Start = First PPT recording (assessed 25 to 30 seconds after start of contraction)
- Middle = PPT at mid-time of contraction (or the average of the two mid-time values if there was an even number of total assessments)
- End = Final PPT assessment obtained during contraction
- Following = PPT recorded postexercise (10 minutes after contraction)

Ratings of pain and fatigue/exertion were performed before the experiment, directly after, and 5 minutes after isometric muscle contraction.

Data Analyses and Statistics

Statistica v. 12.0 (StatSoft AB) software was used for analysis of the data. Parametric statistical methods were used for normally distributed data on a continuous scale, while nonparametric statistics were used for data that were not normally distributed or that were on an ordinal scale. Mean and standard deviation (SD) were used for descriptive statistics for normally distributed data. Median and interquartile range (IQR) were used for descriptive statistics of not normally distributed data. $P < .05$ was considered statistically significant (2-tailed test).

Group differences in baseline PPT, MVF (bite force and grip force), and age were analyzed using analysis of variance (ANOVA), whereas pain intensity was analyzed using the Kruskall-Wallis test. To obtain relative changes, PPTs assessed in the EIH experiment were normalized by dividing the PPT at each time point (before, start, middle, end, and following) by the baseline value. A step-wise method of analyzing the normalized PPT data was adopted.[14] First, three-way repeated measures ANOVA (RM ANOVA) was used for analyses of PPT changes during and after contraction (separately for contraction of the MA and BR). Group (patients and controls) was used as the between-subject variable, while muscle (contracting muscle and resting ipsilateral distant muscle) and time (before, during [start, middle, and end], and following contraction) were used as the within-subject variables. If any interactions were significant, two-way RM ANOVA was used to further explore these. If interactions still existed between group and time, one-way RM ANOVA with Tukey test for multiple comparisons was used as a post hoc test to analyze group differences at certain time points. Finally, the Dunnett test for multiple comparisons vs a control group (ie, before contraction) was used for post hoc analyses of changes with time in each group. Duration of contractions was compared between groups with the Kruskall-Wallis test and the Dunn method as the post hoc test, and the number of subjects in each group that could endure 5-minute contraction was compared using the chi-square test.

Pain intensity in the pain amplification experiment, as well as ratings of pain and fatigue/exertion during contraction, were assessed for each group separately with the Friedman test. For group comparisons, the Kruskall-Wallis test with Dunn all pairwise multiple comparisons as the post hoc test was used for each time point separately. As there were a total of six comparisons made for these variables, Bonferroni correction was used to compensate for multiple comparisons, giving a significance level of $P < .008$. The within-group influence of contractions on ratings of pain and fatigue/exertion was analyzed using the Friedman test. To compare pain intensities and fatigue at different time points between groups, the Kruskall-Wallis test with Dunn all pairwise multiple comparisons as the post hoc test was used for each time point separately (30 to 120 seconds). For all group comparisons, healthy men were compared to healthy women, and healthy women to women with TMD.

Table 1 Background Data in Patients with Temporomandibular Disorder (TMD) Myalgia, Healthy Women, and Healthy Men

Variables	TMD (n = 20)	Women (n = 17)	Men (n = 16)	*P* value
Age (y), mean ± SD	27.5 ± 5.2	28.5 ± 5.5	27.3 (5.0)	.788
Pain duration (y), mean ± SD	5.6 ± 4.8			
CPI (0–100), median (IQR)	47 (27)	0 (0)	0 (0)	
Depression (PHQ-9), median (IQR)	5 (4)			
Anxiety (GAD-7), median (IQR)	4 (4)			
Physical symptoms (PHQ-15), median (IQR)	7 (7)			
PPT (kPa), mean ± SD				
Masseter	128 ± 40	160 ± 52	233 ± 58[b]	**.000**
Brachioradialis	330 ± 121	454 ± 171[a]	383 ± 142	**.043**
MVF				
Masseter (N), mean ± SD	253 ± 132	343 ± 160	596 ± 176[b]	**.000**
Brachioradialis (kg), mean ± SD	21.7 ± 5.8	24.6 ± 4.5	44.1 ± 4.8[b]	**.000**

PPT and MVF were recorded on the most painful side in the patients and on the right or left side (alternating order) in the healthy individuals.
Significant differences according to ANOVA (P < .05) are bolded.
[a]Significant difference compared to TMD. [b]Significant difference compared to healthy women (*P* < .05).
SD = standard deviation; IQR = interquartile range; CPI = characteristic pain intensity (mean of current and worst as well as average pain intensity during the last 2 weeks x 10); PHQ = Patient History Questionnaire; GAD = Generalized Anxiety Disorder; PPT = pressure pain threshold; MVF = maximum voluntary force.

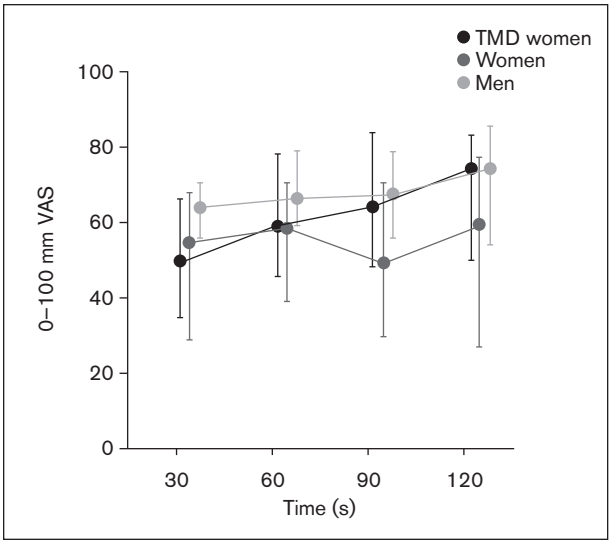

Fig 2 Pain intensity on a 0–100 mm visual analog scale (VAS) induced by repeated application of a painful mechanical pressure every 30 seconds in healthy women (n = 17) and men (n= 16), as well as in female patients with TMD myalgia (n = 20). The pain intensity increased in the patients (Friedman test; *P* < .001), but not in healthy participants (women: *P* = .479; men: *P* = .214). There were no group differences at any time point (Kruskall-Wallis test).

Results

Baseline Characteristics

A total of 17 healthy women and 16 healthy men, as well as 20 female patients with TMD myalgia, participated in the study. Anthropometric data of the participants are shown in Table 1. Baseline PPT at the MA and baseline MVF in both muscles were lower in the healthy women than in the healthy men. Baseline PPT and MVF were lower in the TMD myalgia patients than in the healthy women.

One of the healthy women had asthma and used a cortisone inhaler; one had thyroid hypofunction and took thyroxin; and three reported allergies. Four of the healthy men reported allergies.

One patient reported continuous TMD pain, and all other patients reported recurrent pain. Seventeen patients (85%) had no or low impaired function due to their TMD pain (ie, grade I or II), and three had moderate limitation (grade III) according to the GCPS. Sixteen of the patients (75%) reported temple headache, and 13 reported other pain areas outside the facial area, most often in the neck and shoulders. Two of the patients reported tinnitus, two used anxiolytic drugs (pregabalin), two reported gastrointestinal problems, one used a beta-3-adrenoceptoragonist for urine bladder problems, one reported asthma and used a cortisone inhaler, and two reported allergies.

Suprathreshold Pressure Pain Sensitivity

The mean + SD pressure applied to the MA that the subjects rated as corresponding to 4 on the CR-10 scale was 302 ± 58 kPa in the healthy men, 182 ± 56 kPa in the healthy women, and 127 ± 40 kPa in the patients, with significant differences between healthy women and men (*P* < .001), as well as between women with TMD and healthy women (*P* = .005). The mean pressure that corresponded to 7 on the CR-10 scale was 389 ± 102 kPa in the men, 247 ± 95 kPa in the healthy women, and 162 ± 48 kPa in the patients. Healthy men and women differed (*P* < .001) for this variable, as did women with TMD and healthy women (*P* = .009).

Pain Amplification

The pain intensity during the continuous painful mechanical stimulation of the MA showed a different

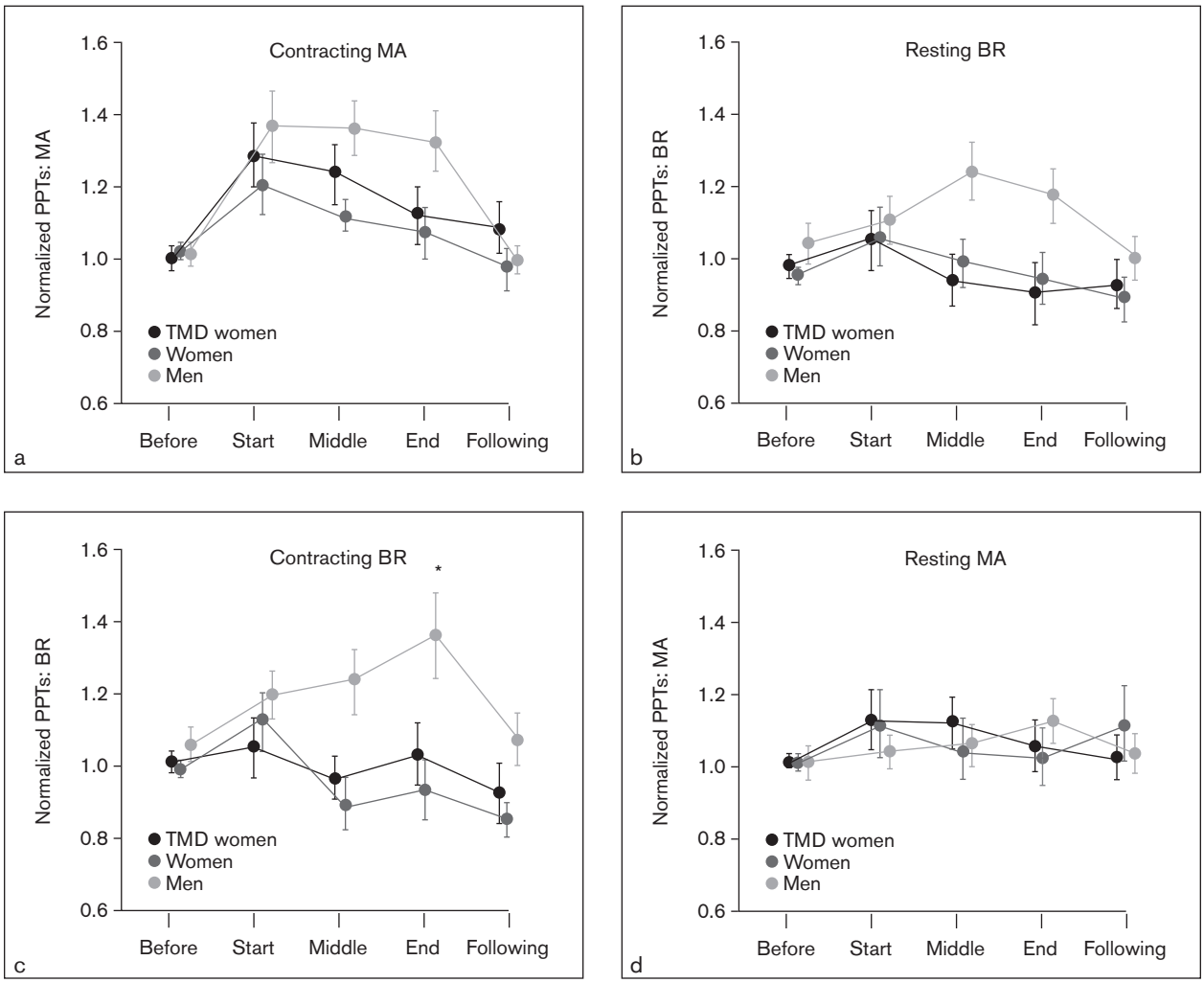

Fig 3 Normalized pressure pain thresholds (PPTs) at baseline (before), during contraction (start, middle, and end), and 10 minutes following contraction of the masseter (MA) and brachioradialis (BR) muscles in female patients with TMD myalgia (n = 20) and in healthy women (n = 17) and men (n = 16). PPTs were normalized by dividing the PPTs of each time point (start, middle, and end) by their baseline value. PPTS at **(a)** contracting MA; **(b)** resting BR (during contraction of the MA); **(c)** contracting BR; and **(d)** resting MA (during contraction of the BR). PPTs at the contracting MA increased during contraction and were significantly increased compared to baseline at the start and middle (Dunnett post hoc test; all $P < .005$); at start in the healthy women ($P = .012$); and at all time points during contraction in the healthy men (Dunnett post hoc test; all $P < .001$). PPTs at the resting BR were increased compared to baseline at the middle and end of contraction (all $P < .043$) in men only. PPTs in the contracting BR also increased during contraction compared to baseline, but this was significant only in the men at the end of contraction ($P = .002$). *Significant difference compared to the healthy women ($P < .05$).

pattern between groups (Fig 2). The median (IQR) pain intensity in the first assessment was 64 (12) in the healthy men, 55 (32) in the healthy women, and 50 (31) in the women with TMD. Pain intensity did not change during the experiment in the healthy participants, but in the patients, pain increased significantly with time. Men in general reported a higher pain intensity to the suprathreshold stimuli than women, but there were no significant group differences at any time point.

PPTs During Contraction of the Masseter

Changes in PPTs during MA contraction are shown in Figs 3a and 3b. The PPTs increased during contraction but had returned to baseline values 10 minutes thereafter (following). The three-way ANOVA showed a significant difference between muscles ($F = 20.28$, $P < .001$) and times ($F = 16.02$, $P < .001$), as well as interactions between group and time ($F = 2.51$, $P = .013$) and between muscle and time ($F = 6.02$, $P < .001$). In the contracting MA, the two-way ANOVA showed a difference between times ($F = 19.68$, $P < .001$) and a tendency toward an interaction between group and time ($F = 1.87$, $P = .067$). In the resting BR, there was a difference between times ($F = 4.53$, $P = .002$) and an interaction between group and time ($F = 2.03$, $P = .045$). However, the Tukey post hoc test revealed no group difference at any time point (Fig 3b).

Table 2 Participants who Endured Continuous Contraction of the Masseter and Brachioradialis Muscles for 5 minutes and Endurance Time

Variables	TMD (n = 20)	Women (n = 17)	Men (n = 16)	*P* value
Masseter				
Endure 5 min, n (%)	9 (45)	11 (65)	0 (0)	**.001**
Time, median (IQR)	270 (173)	300 (105)	133 (82)[a]	**.003**
Brachioradialis				
Endure 5 min, n (%)	11 (55)	13 (76)	3 (19)	**.001**
Time, median (IQR)	300 (150)	300 (130)	203 (76)[a]	**.016**

Significant differences according to chi-square or Kruskall-Wallis test ($P < .05$) are in bold.
[a]Significant difference compared to healthy women (Dunn's post hoc test, $P < .05$).

Table 3 Pain Intensity and Fatigue Before (Bef), Directly After (End), and 5 Minutes After (Aft) Continuous Contraction of the Masseter and Brachioradialis Muscles in Temporomandibular Disorder (TMD) Myalgia Patients and Healthy Subjects

	Pain intensity (Borg CR-10 scale), median (IQR)				Fatigue (Borg RPE scale), median (IQR)			
	Bef	End	Aft	*P* value	Bef	End	Aft	*P* value
Masseter								
TMD	3 (3)	6 (3)	3 (4)	**< .001**	13 (3)	15 (4)	13 (1)	**< .001**
Women	0 (0)[a]	3 (1)[a]	1 (1)[a]	**< .001**	8 (7)[a]	13 (2)[a]	9 (4)[a]	**< .001**
Men	0 (0)	3 (2)	1 (1)	**< .001**	6 (0)	13 (4)	11 (5)	**< .001**
P value	**< .001**	**< .001**	**< .001**		**< .000**	**.004**	**< .001**	
Brachioradialis								
TMD	0 (0)	4 (5)	3 (4)	**< .001**	6 (2)	15 (5)	11 (4)	**< .001**
Women	0 (0)	2 (2)	1 (2)	**< .001**	6 (0)	11 (4)	9 (3)	**< .001**
Men	0 (0)	2 (2)	1 (2)	**< .001**	6 (0)	12 (3)	8 (4)	**< .001**
P value	.027	.033	.023		.342	.039	.023	

Bold *P* values denote significant differences (Friedman ANOVA corrected for multiple comparison; $P < .008$).
[a]Significant difference compared to TMD according to post hoc test ($P < .05$).
NRS = numeric rating scale.

PPTs During Contraction of the BR

Changes in PPTs during contraction of the BR are shown in Figs 3c and 3d. PPTs increased in the contracting BR during contractions. The three-way ANOVA showed a significant time difference ($F = 4.22$, $P = .003$), an interaction between group and muscle ($F = 4.12$, $P = .022$), and an interaction between muscle and time ($F = 2.48$, $P = .046$). In the contracting BR, the two-way ANOVA showed a group difference ($F = 4.11$, $P = .022$), a time difference ($F = 5.77$, $P < .001$), and an interaction between group and time ($F = 2.49$, $P = .013$). The changes of PPTs were significantly higher in the healthy men than in the healthy women at the end of contractions ($P = .009$). In the resting MA, there were no significant changes in PPT.

Duration of Contractions

The number of participants who could endure continuous contraction of the muscles and their contraction times differed between groups for both the MA and BR. There were fewer men that could endure the 5-minute task and their times were significantly shorter compared to the healthy women during contraction of both muscles, but there were no differences between patients and healthy women (Table 2).

Ratings of Perceived Pain and Fatigue During Contraction

Pain intensity and fatigue during contraction is shown in Table 3. Pain intensity in the MA before contraction was significantly higher in the patients than in the healthy women, whereas pain intensity in the BR did not differ between groups. Contraction of the muscle evoked mild pain in the contracting muscle in the healthy participants and increased pain in the contracting muscle in the patients, and significantly higher pain intensity occurred in the women with TMD compared to the healthy women. Pain had not yet returned to baseline values 5 minutes after contraction.

Baseline fatigue did not differ between groups in any of the muscles (Table 3). Fatigue in the contracting muscle increased in all groups during contraction of both the MA and BR. The level of fatigue was higher in the patients than in the healthy women at all time points.

Discussion

To the authors' knowledge, this is the first study that has shown that tooth clenching until exhaustion activates pain inhibition systems locally, as reflected in the increased pain thresholds in the MA in pain-free participants of both sexes and in female TMD myalgia patients. In the healthy men, the pain thresholds also increased remotely in the relaxed BR muscle, while this was not seen in the healthy women or those with TMD. Also, contraction of the pain-free BR activated pain inhibition locally in all groups, but not remotely. However, the magnitude of EIH was more pronounced in healthy men than in healthy women, while healthy women and women with TMD had more similar EIH magnitudes. Furthermore, continuous painful mechanical pressure of the MA led to

amplification of pain in the women with TMD, but not in the healthy women or men.

Activation of EIH

Several previous studies have shown that muscle contraction until exhaustion of spinal muscles activates pain inhibitory systems both locally and remotely in pain-free individuals.[13,14,22] It is therefore interesting that, in the present study, tooth clenching (ie, static contraction of the much smaller jaw-closing muscles) led to EIH. The results are especially interesting in view of the association between self-reported bruxism and TMD pain found in many epidemiologic studies,[23–25] although a cause-effect relationship cannot be determined in such studies. Indeed, most experimental studies have shown that tooth clenching or grinding with varying force levels only causes short-lasting pain.[26] On the other hand, in a recent prospective study, self-reported oral parafunctions were the strongest risk factors for the incidence of TMD in multivariate analysis,[27] indeed pointing to a cause-effect relationship. However, the level of muscle activity may influence the results. Lavigne et al showed 20 years ago that TMD patients with high muscle activity at night reported lower pain intensity than patients with low activity.[28] One may thus speculate that nightly bruxers with high muscle activity may activate pain inhibitory pathways to suppress pain, while sustained tooth clenching at a low level could perhaps lead to pain due to an inability to activate EIH. As muscle motor units are recruited in a relatively fixed order, starting with motor units with smaller receptive fields (Henneman's size principle),[29] sustained low-level contractions would activate the same motor units. These motor units may become overloaded with time, which could ultimately lead to cellular damage. In favor of this view is an experimental clenching study showing reduced PPTs on the day after sustained tooth clenching at a very low level of intensity (7.5%), but not at higher intensities (10% to 40%).[30]

In the present study, tooth clenching did not activate EIH remotely in women with TMD or in healthy women. It may be speculated that smaller jaw muscles may explain the lack of a generalized effect, as the effect on the body as a whole may be less compared to larger muscles. However, the men were able to activate EIH in the relaxed BR during contraction of the MA. As the men had a higher MVF, their mean force used during clenching was higher. It is possible that remote pain inhibition in healthy persons needs a certain force level to be activated. One study in healthy volunteers reported that EIH was activated in response to 30 minutes of aerobic exercise at 75%, but not at 50% of maximal oxygen uptake.[6] Even if static clenching is not an aerobic exercise, these results might support this view.

Sex Differences in EIH and Pain Sensitivity

The pain-free women had less effective pain inhibition than the men during contraction of the MA and BR; this finding supports previous results of less efficient CPM in women.[9] A possible explanation of the sex difference could be that the men put forth more effort during MVF testing than the women, giving a higher relative force during contraction. Higher force levels would exhaust the muscles more rapidly; indeed, the men had shorter endurance time during contraction of both muscles compared to the women. However, other studies have reported a better hypoalgesic effect in women than in men after aerobic[31] and isometric exercise.[32] Different methodologies may perhaps explain these differences.

A higher sensitivity to pressure was seen in the pain-free MA of the healthy women than in the healthy men in this study. However, the men reported higher pain intensity to the constant painful pressure than the women, which was unexpected. The painful pressure used in this experiment roughly corresponded to 50/100 on the VAS. In the women, the median pain intensity at the first recording was 55/100, which shows that the pressure level was accurate. The men, on the other hand, assessed pain intensity higher than was aimed, at 64/100. Therefore, they seem to have underestimated the pain intensity when the painful pressure was determined; ie, a higher pressure was used to evoke pain. Also, the MVF during clenching of the teeth and fist was considerably higher in the men. Men's greater muscle strength (and mass) compared to women's may explain this, but gender roles developed due to social learning may be an additional explanation of both these findings.[33,34] Hypothetically, men may be more prone than women to make a greater effort to contract their muscles with maximum strength.

EIH in TMD

There were no differences in the magnitude of EIH between women with TMD and pain-free women; ie, both groups achieved pain inhibition. This indicates that patients with TMD myalgia have normal function of this pain inhibitory system. This was surprising and opposite to previous findings of a dysfunctional pain inhibition in TMD myalgia,[11,12,35] as well as in many other chronic pain conditions.[5,10,15,16,36] However, even if there are indications that CPM and EIH use similar mechanisms,[37] results regarding EIH in patients with chronic pain also differ across studies. Patients with fibromyalgia show dysfunctional EIH locally and remotely, independent of which muscle is contracting.[13,14,16] On the other hand, patients with localized shoulder myalgia showed dysfunctional local and remote EIH when the painful muscle was contracted, but not during contraction of a pain-free

muscle,[14] while in the present study only local EIH was found. On the contrary, patients with joint pain, osteoarthritis, and rheumatoid arthritis show normal EIH locally.[21,38,39] Hence, different mechanisms may be responsible for EIH in different patient groups. Also, TMD populations differ, as a recent study identified three clusters among individuals with TMD and healthy controls—one adaptive, one pain-sensitive, and one global symptoms cluster.[40] The patients in the present study showed reduced PPTs but little psychological distress and would therefore be more likely to belong to the pain-sensitive group than the global symptoms group. As neither EIH nor CPM was reported as an outcome variable in the former study, it is not known whether the pain-sensitive group and the global symptoms group differed with respect to EIH or CPM.

The present study's finding of chronic pain in the TMD group in spite of normal EIH may be explained by the balance between excitation and inhibition being shifted toward pain amplification. In TMD, there is evidence of ongoing peripheral sensitization in painful muscles.[41–44] Static muscle contraction, such as tooth clenching, may cause muscle ischemia with ensuing release of sensitizing substances and reduced muscle blood flow, as has been reported in other chronic myalgias.[45,46] This may partly explain the ongoing pain and lower baseline PPT in the MA of the TMD group in the present study. However, baseline PPTs were also lower in the remote, pain-free BR,[14] indicating that central mechanisms also participate. Indeed, only the women with TMD showed amplification of their MA pain during application of a continuous painful pressure, which supports the involvement of pain-facilitatory mechanisms at brainstem or higher brain levels. Descending pain-facilitatory mechanisms may also be involved.[2] Thus, neuroplastic central nervous system changes may shift the balance between pain amplification and pain inhibition toward pain amplification in TMD myalgia. In other words, despite the TMD women being able to activate EIH similarly to pain-free women, this activation may still not be sufficient to inhibit their pain.

Even if pain and fatigue in the MA increased in all three groups during contractions in the present study, the patients reported higher pain intensity and fatigue in the MA than in the healthy women at all time points before and after contraction of the MA. This is in accordance with findings in other muscles.[13,15,22] In contrast, there was no difference between groups in pain or fatigue levels during contraction of the pain-free BR; this finding supports the view that pain was localized in the women with TMD.

Study Limitations

This study had some potential limitations. The power analysis was calculated for a slightly larger group, and groups were not proportionate in size, which might have influenced the results. On the other hand, a change of PPTs during static contraction was the main outcome, and the results would probably not have been very different if a few more healthy participants had been recruited.

In addition, the experiments were not performed at the same time point in all participants, as this was not possible for practical reasons. It is not known if diurnal variation affects EIH, but this could be a potential shortcoming.

The results also cannot be generalized to a male TMD population, since, as women are overrepresented among TMD patients, only female patients were recruited, and it was regarded as relevant to only include female TMD myalgia patients and to compare them to the female healthy participants. Thus, future studies including male participants are needed to address this matter and to explore whether there are sex differences in EIH in TMD patients. Last, this study did not control for menstrual cycle variations. Some previous studies have shown differences in endogenous pain inhibition across the menstrual cycle in women.[12,47,48] However, even if sex hormone levels may affect pain inhibition, their influence should not be overestimated, since the inter-individual variation is probably greater.

Conclusions

This study showed that tooth clenching until exhaustion could activate EIH in the contracting MA. Furthermore, the magnitude of EIH was similar in women with TMD myalgia and pain-free women, indicating no deficient EIH was present in TMD women. However, only TMD women showed pain amplification in the MA during application of a continuous painful pressure, which indicates that nociceptive input might drive pain despite normal EIH.

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