The Effect of Nonstrenuous Aerobic Exercise in Patients with Chronic Masticatory Myalgia

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Submitted August 8, 2018;
accepted September 19, 2018.

Aims: To evaluate the effect of nonstrenuous aerobic exercise on chronic masticatory myalgia (CMM) patients and healthy controls (HC) by means of mechanical temporal summation (TS) and response to mechanical stimulation (RMS) performed on the dominant forearm. **Methods:** A total of 30 patients diagnosed with CMM and 30 pain-free HCs were first evaluated for maximum number of steps (MNS) on a stepper machine for 1 minute. Additionally, they completed the Generalized Anxiety Disorder (GAD-7), Graded Chronic Pain Scale (GCPS), and Jaw Functional Limitation Scale (JFL) questionnaires. On the second visit, RMS, mechanical TS, exercise-induced hypoalgesia (EIH), blood pressure, pulse pressure, and heart rate were assessed prior to and immediately, 5, 15, and 30 minutes following 5 minutes of stepper exercise at 50% MNS. **Results:** Compared to HCs, CMM patients demonstrated increased mechanical TS and less efficient EIH. Mechanical TS scores were reduced in both groups; however, the HC reduction was more robust and persistent. CMM patients demonstrated a delayed reduction in RMS following exercise in contrast to an immediate reduction in HCs. GAD-7, GCPS, and JFL scores for CMM patients were higher than for HCs and were associated with baseline pain intensity but not with EIH or TS. **Conclusion:** These findings suggest that, compared to HC, CMM patients' pain modulation is both suppressed and has a different effect duration and timing pattern. Further research should explore the mechanisms and clinical relevance of the delayed hypoalgesia and the inhibitory effect on TS induced by nonstrenuous aerobic exercise in CMM patients. *J Oral Facial Pain Headache 2019;33:143–152. doi: 10.11607/ofph.2342*

Keywords: *exercise, masticatory myalgia, myofascial pain, pain modulation, temporomandibular disorders*

Temporomandibular disorders (TMD) are considered the most common nonodontogenic orofacial pain condition,[1,2] with an estimated prevalence of 5% to 12%. The term TMD refers to a group of conditions that include masticatory muscle myalgia and temporomandibular joint (TMJ) pathologies. While muscle pain is probably more common than joint disorders, the exact prevalence of chronic masticatory myalgia (CMM) is unclear because epidemiologic studies vary in their classifications of muscle and joint disorders.[3–5]

CMM pathophysiology is multifactorial and has been associated with various factors such as stress, genetics, and trauma, among others.[6] CMM typically presents with tenderness to palpation and is further characterized by palpation-induced pain referral locally (within muscle boundaries) or to distant sites such as the ears, teeth, supraorbital area, temporal areas, or neck.[3,7,8] The pain patterns can vary—the pain may peak on awakening or in the evening, and jaw function such as mastication and yawning can either aggravate or alleviate pain.[1,3,5] Treatment modalities include pharmacologic and behavioral treatments, trigger point injections, orthotic appliances, and physical therapy.[5,9–12] Nevertheless, there is no gold standard or one recognized treatment protocol.

It is broadly accepted that physical activity is favorable to an individual's overall health,[13] as well as in the treatment and rehabilitation of patients with chronic pain.[14] Exercise or physical activity can reduce

pain sensitivity, but this effect varies between subjects.[15,16] The decreased sensitivity to painful stimuli induced by exercise is termed exercise-induced anesthesia or exercise-induced hypoalgesia (EIH).[17–19] Exercise protocols that can demonstrate a hypoalgesic effect include isometric muscle contraction (a static contraction with no joint movement), aerobic exercise (such as running), or dynamic resistance exercises (muscle contractions that produce joint movements).[14] The extent of hypoalgesia has been shown to be related to the exercise type, intensity, and duration.[14,20] Consequently, exercise is incorporated into treatment protocols for painful chronic conditions such as fibromyalgia, chronic fatigue, arthritis, and low back pain.[21–26]

The exact mechanism underlying EIH is still not fully understood; however, exercise is known to activate inhibitory pain modulation systems such as the release of peripheral and central endorphins[14,27–30] and neurotransmitters such as serotonin, norepinephrine, and endocannabinoids.[31] Interaction with the cardiovascular system has also been mentioned as a potential mechanism.[32,33]

Various chronic pain conditions such as fibromyalgia, tension-type headache, migraine, chronic low back pain, irritable bowel syndrome, and burning mouth syndrome have all been shown to be associated with faulty pain modulation—specifically, deficient pain inhibition.[34–39] Pain modulation studies involving TMD and CMM patients employing methods other than exercise revealed conflicting findings, ranging from systemic altered pain modulation[40] to localized alteration[41] to no alteration in pain modulation.[42,43] A recent systematic review concluded that increased pain facilitation and a trend for pain inhibition impairment exist in nonparoxysmal orofacial pain patients.[44]

However, exercise can also induce or augment existing pain, especially in patients suffering from a chronic pain condition.[16,45,46] This may affect patient compliance with a protocol that includes intense exercise. Low-intensity exercise is probably less efficient, but has been shown to be effective in alleviating muscle pain in an animal model.[47]

The objective of this study was to evaluate the role of a nonstrenuous, low-intensity aerobic exercise protocol in CMM patients. It was hypothesized that patients suffering from CMM would present less efficient EIH compared to healthy individuals.

Materials and Methods

Patient Recruitment and Study Overview

This study was conducted at the Center for Temporomandibular Disorders and Orofacial Pain, Department of Diagnostic Sciences, Rutgers School of Dental Medicine, Newark, New Jersey and was approved by the Rutgers Internal Review Board (Pro20150002391).

A detailed explanation of the study and procedures was provided to each participant, and signed consent forms were obtained. The study group included patients suffering from masticatory myalgia (local or myofascial pain with referral) for more than 3 months. Diagnoses were made based on the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).[8,48] The healthy control (HC) group included healthy individuals matched for age and gender to the study group. All of the subjects involved in the study were 18 years or older and could communicate, understand, and follow the study instructions. Pregnant women, patients under active treatment for chronic pain, and patients suffering from systemic diseases that can either prevent them from exercising or have an effect on the patients' nervous systems were excluded from the study.

During the first visit, general information such as age, sex, ethnicity, and medical history were collected, and body mass index (BMI) was calculated. The Generalized Anxiety Disorder (GAD-7),[49] Graded Chronic Pain Scale (GCPS),[8] and Jaw Functional Limitation Scale (JFL)[50–52] questionnaires were completed by each participant. Maximum number of steps (MNS) during 1 minute on a stepper (Duro-Med Mini Stepper Exerciser, Model: 660-2005-0000, 1504-242) was measured, and an exercise protocol training session as well as a practice sensory testing session were performed.

During the second visit, response to mechanical stimulation (RMS), mechanical temporal summation (TS), exercise-induced hypoalgesia (EIH), blood pressure, and pulse rate were assessed before and immediately, 5, 15, and 30 minutes following 5-minute stepper exercises at 50% MNS. The examiner was blind to the patient groups. The study flowchart (Fig 1) illustrates the tests and procedures performed during the first and second visits.

Assessment of Response to Mechanical Stimulation and TS

Mechanical TS was assessed using a von Frey monofilament (No. 5.46, Stoelting) delivering a force of 26 g. The test was performed on the middle portion of the subject's dominant volar forearm before and immediately, 5, 15, and 30 minutes following the exercise. A single stimulus and then 29 successive stimuli were applied within an area of 1 cm in diameter using the same filament. For each session, the area selected for the repeated stimuli was slightly different, and the stimuli were applied at 1-second intervals. An 11-point numeric pain scale (NPS) from 0 to 10 was used for reporting pain intensity at the

1st, 10th, 20th, and 30th stimuli. The difference between the 1st and the 30th stimulus scores was considered the mechanical TS score.[53,54] The subjects' response to the first stimulus (a single stimulus with no summation effect) before and immediately, 5, 15, and 30 minutes following the exercise was recorded as the RMS.

Exercise Protocol and EIH Assessment

EIH was induced by a nonstrenuous step exercise. At the first visit, subjects were instructed to step the maximum number of steps (MNS) that they were able to in 1 minute, and from this, 50% MNS was calculated (MNS_{50}). All study participants were requested to exercise on the stepper at MNS_{50} for a 5-minute session while a digital metronome (Pro Metronome, 3.13.2, EUM Lab) assisted the participants in synchronizing and maintaining the pace of their steps at MNS_{50} for the entire session. EIH was calculated as the difference between the TS after and prior to (baseline) exercise and was evaluated at four time points: immediately and 5 minutes, 15 minutes, and 30 minutes after the exercise. Negative EIH values indicate more efficient pain reduction.

Physiologic Parameters

Systolic and diastolic blood pressure along with heart rate were measured using FDA-approved standard equipment (Wrist-type Fully Automatic Digital Blood Pressure Monitor, Model BP-202H) during the first visit. During the second visit, blood pressure and heart rate were assessed at baseline and immediately, 5, 15, and 30 minutes following the exercise. Pulse pressure for each time point measurement was calculated as the difference between the systolic and diastolic blood pressures. The subjects' weights were measured using Smart Scale (1byone Wellness Smart Scale, Model: 700NA-0006), and height was measured using height indicator tape (KC Professional 16 ft 3/4" Power Tape, Model: 90018). BMI was calculated as body mass (kg) divided by the square of the body height (m).

Questionnaires and Pain Assessment

Anxiety was evaluated during the first visit using the GAD-7 questionnaire, and the subjects were categorized based on the total score as having mild (5–9), moderate (10–14), or severe (≥ 15) anxiety. JFLS and GCPS questionnaire scores were also obtained at the first visit. Pain intensity was assessed with the 11-point NPS during both visits in response to the mechanical stimulation before and after exercise, as described earlier. Baseline NPS scores were categorized as mild (1–3), moderate (4–6), or severe (7–9) to allow comparisons with GAD-7 and JFLS scores.[55,56]

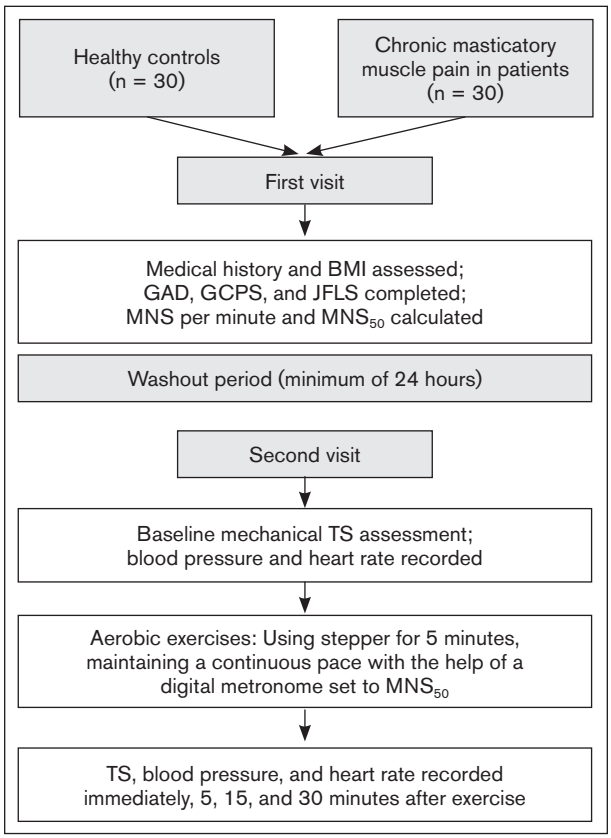

Fig 1 Study flowchart. BMI = body mass index; GAD-7 = Generalized Anxiety Disorder-7; GCPS = Graded Chronic Pain Scale; JFLS = Jaw Function Limitation Scale; MNS = maximum number of steps; MNS_{50} = 50% of MNS; TS = temporal summation.

Data Analyses

The outcome measures distributions were tested for normality using the Shapiro-Wilk test. The results indicated that the TS, EIH, RMS, GCPS, NRS, and BMI outcomes were significantly skewed. Therefore, nonparametric approaches, such as the Wilcoxon rank sum test, were used to compare the medians of the two groups (CMM and HC). In the CMM group, GAD-7 and NPS scores were divided into mild, moderate, or severe, and the exact Kruskal-Wallis test was used to compare the medians across the groups. The Steel-Dwass multiple comparisons method was used to control the overall type I error in pairwise comparisons. The nonparametric Wilcoxon test was used to analyze repeated outcomes within the group. For normally distributed outcomes, Student *t* test was used to compare the means of the CMM and HC groups, and multivariate analysis of variance (MANOVA) was used for the analysis of repeated measures data. Analysis of variance (ANOVA) was used to compare the means across multiple groups with Tukey multiple comparisons method to control the overall type I error in pairwise comparisons. The alpha was set at .05. Statistical analyses were performed using JMP Pro 13.0.0 (SAS Institute).

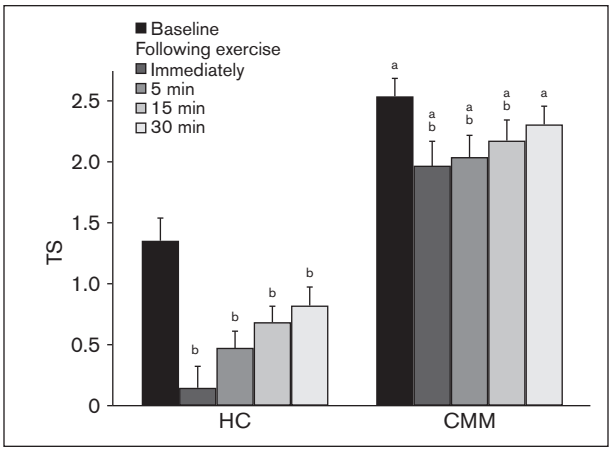

Fig 2 Mechanical temporal summation (TS) in the CMM and HC groups. Data are presented as mean ± standard error of the mean. In both the CMM and HC groups, the response to the 30th stimulus was significantly higher than the 1st stimulus. [a]Significant difference between groups ($P < .001$). [b]Significant reduction in TS score compared to baseline ($P < .006$).

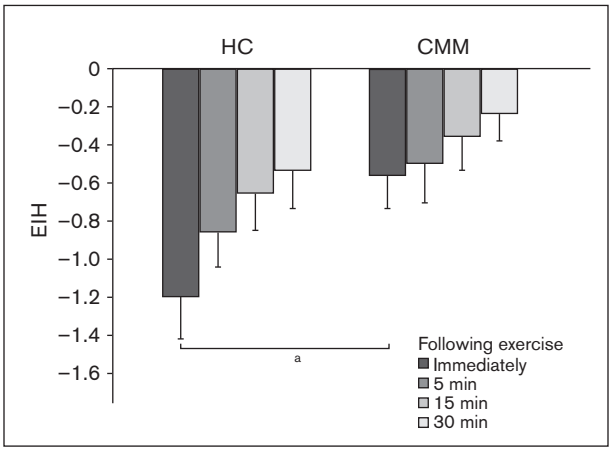

Fig 3 Exercise-induced hypoalgesia (EIH) in the CMM and HC groups. Data are presented as mean ± standard error of the mean. [a]Significant difference ($P = .003$).

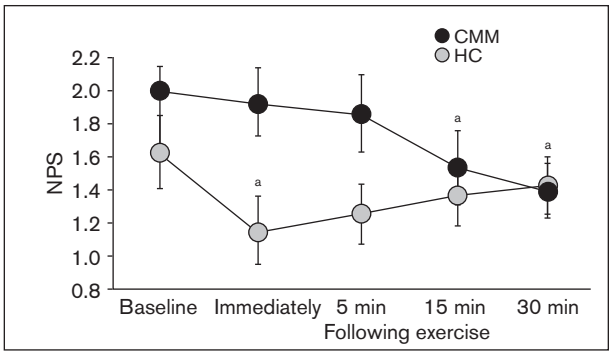

Fig 4 Patient response to mechanical stimulation (RMS), quantified by a numeric pain scale (NPS), to a single 26-g stimulus before and immediately, 5, 15, and 30 minutes following the exercise. Data are presented as mean ± standard error of the mean. [a]Significant reduction compared to baseline ($P < .05$).

Results

A total of 60 subjects were included in this study: 30 in the CMM group and 30 in the HC group. The CMM group was comprised of 21 women and 9 men, and the HC group of 17 women and 13 men. The mean age of patients in the CMM group was 33.13 ± 9.93 years (range 23 to 60) and of the subjects in the HC group was 32.9 ± 8.87 years (range 25 to 56) ($P = .96$).

Effects of Exercise on TS

At baseline, a significant summation effect was observed in both the CMM and HC groups: the response to the 30th stimulus was significantly higher compared to the 1st stimulus ($P < .0001$). CMM patients had a significantly higher TS score compared to the HC group ($P < .001$) at all time points before and after exercise (Fig 2). Age and gender had no significant effect on TS in either group ($P > .05$).

Exercise had a significant inhibitory effect on TS in both groups. The effect in the HC group was more robust immediately following the exercise (comparison of percent changes from baseline, $P < .05$) and lasted longer. In both groups, significant reduction in the TS score compared to baseline was observed immediately, 5 minutes, and 15 minutes following the exercise; however, while significant reduction was still observed after 30 minutes ($P = .006$) in the HC group, in the CMM group, the effect on TS diminished and was no longer significantly different compared to baseline 30 minutes following exercise ($P = .1$) (Fig 2).

Exercise-Induced Hypoalgesia

The CMM group demonstrated significantly less efficient EIH (difference between the TS after and prior to exercise) compared to the HC group immediately following the exercise ($P = .003$) (Fig 3). There was no significant difference in EIH evaluated at 5, 15, or 30 minutes following exercise between the CMM and HC groups ($P > .05$). No significant differences in EIH were found between men and women immediately, 5, 15, or 30 minutes after exercise in either the CMM or HC group ($P > .05$), and age had no significant effect on EIH in either group ($P > .05$).

Effects of Exercise on RMS

RMS (response to the 1st stimulus) in the HC group significantly decreased following exercise ($P = .0362$) and gradually returned to baseline levels 15 and 30 minutes following exercise. In the CMM group, the RMS decreased significantly compared to baseline scores at 15 ($P = .02$) and 30 ($P = .0001$) minutes following exercise (Fig 4).

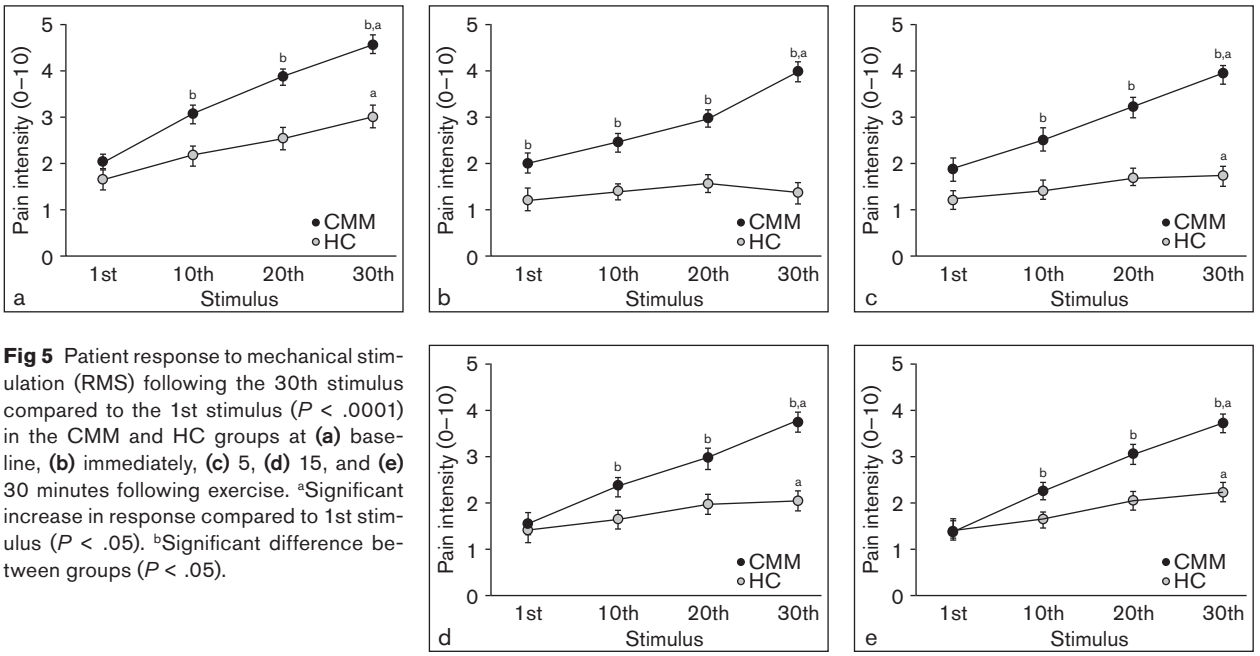

Fig 5 Patient response to mechanical stimulation (RMS) following the 30th stimulus compared to the 1st stimulus ($P < .0001$) in the CMM and HC groups at **(a)** baseline, **(b)** immediately, **(c)** 5, **(d)** 15, and **(e)** 30 minutes following exercise. [a]Significant increase in response compared to 1st stimulus ($P < .05$). [b]Significant difference between groups ($P < .05$).

The response to the 30th stimulation in both groups was significantly higher than the 1st stimulus ($P < .0001$) at baseline (Fig 5a) and 5, 15, and 30 minutes following exercise (Figs 5c, 5d, and 5e). Immediately following exercise, the response to the 30th stimulus in the CMM group, but not in the HC group ($P = .8$), was significantly elevated compared to the 1st response ($P < .0001$) (Fig 5b). The pain scores in response to the 10th, 20th, and 30th stimuli were significantly higher in the CMM group compared to the HC at baseline and immediately, 5, 15, and 30 minutes following exercise ($P < .01$).

Physiologic Parameters

The physiologic parameters scored are presented in Table 1.

Body Mass Index. No significant differences were found between the BMI of the CMM and HC groups (Wilcoxon rank sum, $P = .89$).

Diastolic Blood Pressure. Significant differences in diastolic blood pressure were found between the CMM and HC groups at baseline ($P = .02$), immediately ($P = .04$), and 30 minutes ($P = .045$) following exercise. The 5 minutes of nonstrenuous step exercise had no significant effect on diastolic blood pressure in either group ($P = .89$).

Systolic Blood Pressure. No significant differences in systolic blood pressure were found between the CMM and HC groups ($P = .47$). Five minutes of nonstrenuous exercise did not have a significant effect on systolic blood pressure in either group ($P = .99$).

Pulse Pressure. No significant differences in pulse pressure were found between the CMM and HC groups ($P = .52$). Five minutes of nonstrenuous exercise did not have a significant effect on pulse pressure in either group ($P = .82$).

Heart Rate. No significant differences in heart rate were found between the CMM and HC groups ($P = .57$). Five minutes of nonstrenuous exercise did

Table 1 Physiologic Parameters Before and After Nonstrenuous Exercise

	CMM	HC
Baseline		
BMI	25.15 ± 5.91	23.66 ± 2.64
Diastolic blood pressure*	67.17 ± 6.91	71.2 ± 5.52
Systolic blood pressure	106.9 ± 11.87	109.23 ± 7.97
Pulse pressure	39.73 ± 10.7	38.03 ± 6.59
Heart rate	72.5 ± 11.17	73.23 ± 12.2
Immediately after		
Diastolic blood pressure*	67.33 ± 5.71	70.33 ± 5.46
Systolic blood pressure	106.6 ± 11.07	108.17 ± 9.22
Pulse pressure	39.27 ± 8.87	37.83 ± 7.44
Heart rate	72.03 ± 10.63	73.83 ± 11.67
5 min after		
Diastolic blood pressure	67.27 ± 6.16	70 ± 5.25
Systolic blood pressure	105.63 ± 10.63	107.53 ± 10.37
Pulse pressure	38.37 ± 7.34	37.53 ± 8.92
Heart rate	71.03 ± 10.48	73.5 ± 11.95
15 min after		
Diastolic blood pressure	67.33 ± 5.6	69.9 ± 5.33
Systolic blood pressure	105.4 ± 12.63	107.2 ± 9.93
Pulse pressure	38.07 ± 10.36	37.3 ± 7.77
Heart rate	71.57 ± 11.15	73.2 ± 11.64
30 minutes after		
Diastolic blood pressure*	67.23 ± 5.09	70.03 ± 5.53
Systolic blood pressure	106.2 ± 12.11	107.57 ± 11.14
Pulse pressure	38.97 ± 9.35	37.53 ± 10.57
Heart rate	71.67 ± 11.24	73.17 ± 11.79

All data are reported as mean ± standard deviation. BMI = Body Mass Index. *Significant difference ($P < .05$).

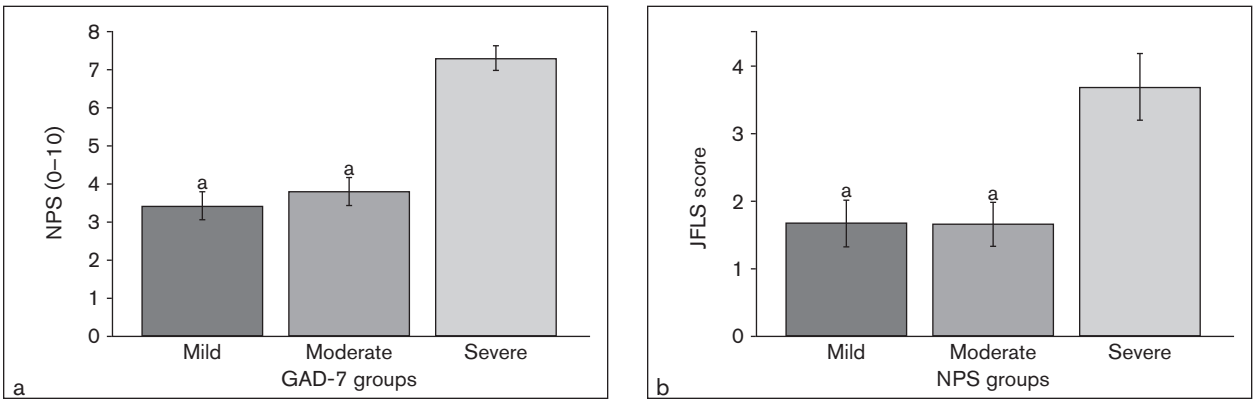

Fig 6 **(a)** Association between pain as rated on a numeric rating scale (NPS) and anxiety as rated on the Generalized Anxiety Disorder-7 (GAD-7), grouped into mild (5–9), moderate (10–14), and severe (15–21). [a]Significant difference compared to severe anxiety. **(b)** Association between pain as rated on NRS, grouped into mild (1–3), moderate (4–6), and severe (7–9), and Jaw Function Limitation Scale (JFLS) scores. [a]Significant diference compared to severe pain.

not have a significant effect on HR in either group ($P = .59$).

Anxiety, Jaw Function, and Pain Status Questionnaires

GAD-7 Score. CMM patients demonstrated significantly higher anxiety as measured by GAD-7 scores compared to the HC group (Student *t* test, $P < .0001$). Because the GAD-7 scores in the HC group were uniformly equal to 0, no further analyses with other outcomes were done in this group. Linear regression analysis did not find a significant association between CMM GAD-7 scores and EIH ($P = .1$) or TS ($P = .8$).

NPS Score at Baseline. CMM patients demonstrated significantly higher NPS scores at baseline compared to HC ($P < .0001$). Because in the HC group NPS scores were uniformly equal to 0, no further analyses with other outcomes were done in this group. Regression analysis did not find a significant association between NPS scores and EIH or TS in the CMM group.

There was a significant association between the GAD-7 scores and NPS in the CMM group ($P = .006$). To further evaluate the association between anxiety levels and pain levels in the CMM group, the GAD-7 scores were grouped into mild (5–9), moderate (10–14), and severe (15–21). Nonparametric comparisons for all pairs using the Steel-Dwass method for multiple comparisons were done to identify significant differences in NPS scores between different levels of anxiety in the CMM group. CMM patients with severe anxiety had significantly higher NPS scores (7.33 ± 0.58) compared to those with moderate (3.8 ± 1.52, $P = .03$) or mild (3.45 ± 1.21, $P = .03$) anxiety (Fig 6a). No significant difference in NPS scores was observed in CMM patients with moderate compared to mild anxiety ($P = .88$).

JFLS Scores. CMM patients demonstrated significantly higher JFLS scores (1.92 ± 1.34) compared to the HC group (0.00 ± 0.00, $P < .0001$). Because the JFLS scores in the HC group were uniformly equal to 0, no further analyses with other outcomes were done in this group. No significant associations between JFLS and EIH or TS were observed in the CMM group. There was a significant association between the JFLS and NPS scores in the CMM group ($P = .01$).

Based on NPS scores, the CMM group was divided into those with mild (1–3), moderate (4–6), and severe (7–9) pain intensity. CMM patients with severe pain had significantly higher JFLS scores (3.67 ± 0.67) compared to moderate (1.64 ± 1.17, $P = .02$) or mild (1.66 ± 1.24, $P = .02$) pain (Fig 6b). No significant differences in JFLS scores were found between the CMM patients with mild and moderate pain (Tukey, $P = 1$).

GCPS Scores. The CMM group demonstrated significantly higher GCPS scores (2.53 ± 0.94) compared to the HC group (0.00 ± 0.00, $P < .0001$). GCPS scores were uniformly equal to 0 in the HC group; therefore, no additional analyses were performed with GCPS in this group. No significant associations between GCPS and EIH, TS, or GAD-7 scores were observed in the CMM group.

Discussion

The etiology of CMM is not fully understood; however, the condition has been associated with anxiety, depression, mood, and stress-related disorders. There is currently no standard treatment for CMM, and the treatments range from pharmacologic and behavioral interventions to trigger point injections, orthotic appliances, and physical therapy. Additionally,

the effectiveness of the available therapies varies widely from patient to patient.[1,5,57] Exercise has been shown in multiple contexts to alleviate different kinds of pain and is incorporated into treatment protocols for a wide range of conditions.[21,23–26] In this study, the role of a nonstrenuous step exercise was evaluated as EIH in CMM patients and healthy controls. Mechanical TS and RMS before and after a 5-minute exercise during which the subject stepped at a rate of half their capable maximum number of steps per minute were measured.

Prior to exercise, it was found that CMM patients exhibited higher baseline mechanical TS, and following exercise, it was found that EIH in the CMM group was less efficient than in the HC group. The augmented response to repeated stimulation and the less efficient modulation of pain demonstrated in CMM patients are in line with previous reports on faulty modulation of pain in patients suffering from other chronic pain conditions.[34–36,53,58,59]

Although exercise is one of the methods commonly used to assess the inhibitory pain modulation system[19,60] and to demonstrate less efficient modulation in chronic pain patients,[46,61–63] the majority of the studies on TMD or CMM patients were performed by employing the conditioned pain modulation (CPM) paradigm, whereby a painful conditioning stimulus inhibits the test stimulus (pain inhibits pain).

EIH and CPM are correlated and share common mechanisms. Both activate the opioid, cannabinoid, serotonergic, noradrenergic, and dopaminergic systems[16,30,31,47,64–66] and interact with the cardiovascular system.[67–69] Moreover, CPM can predict EIH extent in healthy subjects,[70,71] and triathletes appear to have more efficient CPM.[72] Yet, CPM and EIH are not identical. An important difference is the effect duration—while CPM effect is limited to the time at which the conditioning painful stimulus is provided, EIH endures beyond the exercise period.[73] Therefore, the hypoalgesic effect duration is an aspect that can be studied with EIH, but not with CPM.

In this study, differences were found in the effect duration and timing between the groups. Thirty minutes following the nonstrenuous exercise, the TS score in the HC group remained significantly lower than baseline, while in the CMM it returned to baseline. The RMS to a single stimulus in the HC group significantly decreased immediately following the exercise and then gradually returned to baseline levels. In the CMM group, no significant effect was observed immediately following the exercise; however, significant reduction was noted 15 and 30 minutes after the exercise (Fig 4). This suggests that CMM patients' pain modulation is both suppressed and has a different pattern related to the effect duration and timing. It is important to note that this was observed only in a single stimulus RMS, not in the overall EIH or TS effect. The augmented summation and less efficient EIH seen in CMM and other chronic pain conditions may have a masking effect on the probably subtler and delayed positive effect on pain.

Aerobic exercise is successfully incorporated into the management of fibromyalgia[21,74] and other chronic pain syndromes, such as osteoarthritis[75] or rheumatoid arthritis,[76] in spite of minimal hypoalgesia or even occasionally worsening symptoms during or after exercise.[77] The hypoalgesic effect not evident following a single exercise session may develop following repeated sessions. Most of the studies did not evaluate the hypoalgesic effect timing that was demonstrated in this study.

The lack of consistency in the exercise protocols used to study EIH may have led to conflicting findings. Exercise intensity and length have a role in determining the extent of hypoalgesia,[17,78] and differences have also been demonstrated between the effects induced by isometric muscle contraction and aerobic exercise.[79] Longer or more intense exercise protocols can also induce or increase existing pain, mainly in patients suffering from acute or chronic musculoskeletal pain.[16,46] To minimize additional pain induced by exercise in the present study, primarily in the CMM group, a submaximal aerobic exercise protocol was used. Several aerobic exercise protocols were explored, and it was found that 50% maximal activity for 5 minutes on a stepper consistently induced hypoalgesia with minimal discomfort or aches and without a significant increase in blood pressure or heart rate.

Previous studies have shown high-intensity treadmill exercises to be necessary for inducing hypoalgesic effects,[78] whereas the present study shows that a nonstrenuous, submaximal stepper exercise may be enough to induce hypoalgesia in CMM patients. This in turn could make EIH a more attainable reality for patients who have difficulty engaging in intensive exercise for various reasons, including physical or mental barriers. The differences from previous studies may be related to the use of a stepper and not the more commonly used treadmill running, and perhaps also related to the carefully selected intensity and duration of the activity. Furthermore, stepper exercises may involve dynamic resistance exercises in addition to the typical aerobic activity.

An association between pain perception and blood pressure, as well as lower systolic blood pressure during exercise, has been reported in previous studies.[80–82] Aerobic and isometric exercises are often accompanied by an increase in blood pressure and heart rate, and although these rises have been observed in combination with changes in sensitivity to painful stimuli,[83–85] a direct association between

blood pressure and EIH has not been demonstrated.[68,86,87] Significant increases in blood pressure or heart rate were not observed in the current study, probably due to the relatively low-intensity exercise protocol that did not stimulate significant changes in those parameters. Diastolic blood pressure in CMM patients was significantly lower than in HC patients at baseline and following exercise. This finding is in line with a previous report[88] that found similarly lower diastolic blood pressure at rest in CMM patients; it was suggested that this was the result of an increase in peripheral fluid volume and local vasodilation with no increase in the overall volume induced by an increase in norepinephrine, 5-HT, and epinephrine levels at the brainstem.

Significant differences in BMI were not found between the CMM and HC groups; however, it has been suggested in previous studies that obese patients are at a higher risk of developing chronic pain.[89] Therefore, adding exercise to CMM patients' treatment protocols may have a positive effect on their pain levels in addition to a possible positive effect on their overall health.

Contrary to previous studies that demonstrated a reduction in pain modulation efficiency with increased age,[90] no significant associations between either TS or EIH and age were found. This may be related to the fact that 80% of the subjects enrolled in the study were between 25 and 40 years old. Previous studies have demonstrated significant changes in pain modulation in age groups older than those included in the current study.[91]

As expected, the JFLS and GCPS scores were higher in the CMM patients and were associated with the CMM patients' pain scores. However, no associations were found with TS or EIH scores, suggesting different and perhaps independent mechanisms for the hypoalgesic effect induced by exercise.

Various studies show anxiety to be associated with different chronic pain conditions, including CMM and TMD.[92–95] Consequently, higher GAD-7 scores in CMM patients than in controls were found, and among CMM patients, those with severe anxiety (as characterized by an increased GAD-7) also exhibited higher pain scores. Interestingly, similar to the JFLS and GCPS scores, the anxiety levels had no association with either TS or EIH scores.

The inherent study limitations include response bias of the self-report questionnaires, as well as a possible Hawthorne effect of subjects modifying their behavior while being observed during the exercise and assessment of pain and TS. Additionally, the present study sample included a majority of women. It could be of interest for future studies to measure the total duration of the hypoalgesic effects beyond the 30 minutes measured in this study.

Conclusions

The positive effect of exercise on pain shown in this and other studies, as well as its known positive effect on mental health,[96–98] make exercise an enticing treatment modality for CMM patients that should be further explored. However, the lack of an immediate hypoalgesic effect and the potential increase in pain during exercise can contribute to chronic pain patients' low compliance with exercise treatment protocols. Therefore, the recognition that nonstrenuous exercises can induce hypoalgesia and alleviate pain for people afflicted with CMM may facilitate the inclusion of exercise as a treatment protocol and make EIH more accessible to chronic pain patients. A stepper exercise may not be suitable for all; therefore, different protocols and forms of exercise should be explored as well. Further studies are needed to explore the mechanism underlying the delayed analgesic effect demonstrated in CMM patients and its relevance to potential treatment protocols.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or nonprofit sectors. The authors have no conflicts of interest to declare.

References

1. Okeson JP (ed). Bell's Oral and Facial Pain, ed 7. Chicago: Quintessence, 2014.
2. Slade GD, Bair E, Greenspan JD, et al. Signs and symptoms of first-onset TMD and sociodemographic predictors of its development: The OPPERA prospective cohort study. J Pain 2013;14(12 suppl):T20–T32.e1–e3.
3. Mense S, Gerwin RD (eds). Muscle Pain: Diagnosis and Treatment. Heidelberg: Springer, 2010.
4. Karakasis D. The incidence of masticatory dysfunction and its relation to the masticatory myalgia syndrome. J Maxillofac Surg 1977;5:310–313.
5. Svensson P, Sharav Y, Benoliel R. Myalgia, myofascial pain, tension-type headaches, and fibromyalgia. In: Sharav Y, Benoliel R (eds). Orofacial Pain and Headache, ed 2. Chicago: Quintessence, 2015:195–256.
6. Liu F, Steinkeler A. Epidemiology, diagnosis, and treatment of temporomandibular disorders. Dent Clin North Am 2013; 57:465–479.
7. Mense S. Differences between myofascial trigger points and tender points [in German]. Schmerz 2011;25:93–103.
8. Schiffman E, Ohrbach R, Truelove E, et al. Diagnostic Criteria for Temporomandibular Disorders (DC/TMD) for clinical and research applications: Recommendations of the International RDC/TMD Consortium Network* and Orofacial Pain Special Interest Group. J Oral Facial Pain Headache 2014;28:6–27.
9. Schaffer SM, Brismée JM, Sizer PS, Courtney CA. Temporomandibular disorders. Part 2: Conservative management. J Man Manip Ther 2014;22:13–23.
10. Zeno E, Griffin J, Boyd C, Oladehin A, Kasser R. The effects of a home exercise program on pain and perceived dysfunction in a woman with TMD: A case study. Cranio 2001;19:279–288.

11. Fricton J. Myogenous temporomandibular disorders: Diagnostic and management considerations. Dent Clin North Am 2007; 51:61–83.
12. Medlicott MS, Harris SR. A systematic review of the effectiveness of exercise, manual therapy, electrotherapy, relaxation training, and biofeedback in the management of temporomandibular disorder. Phys Ther 2006;86:955–973.
13. Huxley RR. Physical activity: Can there be too much of a good thing? Circulation 2015;131:692–694.
14. Naugle KM, Fillingim RB, Riley JL 3rd. A meta-analytic review of the hypoalgesic effects of exercise. J Pain 2012;13:1139–1150.
15. Landmark T, Romundstad PR, Borchgrevink PC, Kaasa S, Dale O. Longitudinal associations between exercise and pain in the general population—The HUNT pain study. PLoS One 2013;8:e65279.
16. Lima LV, Abner TSS, Sluka KA. Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena. J Physiol 2017;595:4141–4150.
17. Koltyn KF. Analgesia following exercise: A review. Sports Med 2000;29:85–98.
18. Koltyn KF. Exercise-induced hypoalgesia and intensity of exercise. Sports Med 2002;32:477–487.
19. Black J, Chesher GB, Starmer GA, Egger G. The painlessness of the long distance runner. Med J Aust 1979;1:522–523.
20. Smith A, Ritchie C, Pedler A, McCamley K Roberts K, Sterling M. Exercise induced hypoalgesia is elicited by isometric, but not aerobic exercise in individuals with chronic whiplash associated disorders. Scand J Pain 2017;15:14–21.
21. Brosseau L, Wells GA, Tugwell P, et al. Ottawa Panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: Part 1. Phys Ther 2008;88:857–871.
22. Jansen MJ, Viechtbauer W, Lenssen AF, Hendriks EJ, de Bie RA. Strength training alone, exercise therapy alone, and exercise therapy with passive manual mobilisation each reduce pain and disability in people with knee osteoarthritis: A systematic review. J Physiother 2011;57:11–20.
23. Stewart MJ, Maher CG, Refshauge KM, Herbert Rd, Bogduk N, Nicholas M. Randomized controlled trial of exercise for chronic whiplash-associated disorders. Pain 2007;128:59–68.
24. van Middelkoop M, Rubinstein SM, Verhagen AP, Ostelo RW, Koes BW, van Tulder MW. Exercise therapy for chronic nonspecific low-back pain. Best Pract Res Clin Rheumatol 2010; 24:193–204.
25. Fransen M, McConnell S, Hernandez-Molina G, Reichenbach S. Exercise for osteoarthritis of the hip. Cochrane Database Syst Rev 2014;(4):CD007912.
26. Busch AJ, Webber SC, Richards RS, et al. Resistance exercise training for fibromyalgia. Cochrane Database Syst Rev 2013; (12):CD010884.
27. Goldfarb AH, Jamurtas AZ. Beta-endorphin response to exercise. An update. Sports Med 1997;24:8–16.
28. Paulev PE, Thorbøll JE, Nielsen U, et al. Opioid involvement in the perception of pain due to endurance exercise in trained man. Jpn J Physiol 1989;39:67–74.
29. Pertovaara A, Kemppainen P, Johansson G, Karonen SL. Ischemic pain nonsegmentally produces a predominant reduction of pain and thermal sensitivity in man: A selective role for endogenous opioids. Brain Res 1982;251:83–92.
30. Stagg NJ, Mata HP, Ibrahim MM, et al. Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: Role of endogenous opioids. Anesthesiology 2011;114:940–948.
31. Crombie KM, Brellenthin AG, Hillard CJ, Koltyn KF. Endocannabinoid and opioid system interactions in exercise-induced hypoalgesia. Pain Med 2018;19:118–123.
32. Martins DF, Mazzardo-Martins L, Soldi F, Stramosk J, Piovezan AP, Santos AR. High-intensity swimming exercise reduces neuropathic pain in an animal model of complex regional pain syndrome type I: Evidence for a role of the adenosinergic system. Neuroscience 2013;234:69–76.
33. Lovick TA. Integrated activity of cardiovascular and pain regulatory systems: Role in adaptive behavioural responses. Prog Neurobiol 1993;40:631–644.
34. Kennedy DL, Kemp HI, Ridout D, Yarnitsky D, Rice AS. Reliability of conditioned pain modulation: A systematic review. Pain 2016;157:2410–2419.
35. Nasri-Heir C, Shigdar D, Alnaas D, Korczeniewska OA, Eliav R, Heir GM. Primary burning mouth syndrome: Literature review and preliminary findings suggesting possible association with pain modulation. Quintessence Int 2017:49–60.
36. Nir RR, Yarnitsky D. Conditioned pain modulation. Curr Opin Support Palliat Care 2015;9:131–137.
37. Yarnitsky D, Bouhassira D, Drewes AM, et al. Recommendations on practice of conditioned pain modulation (CPM) testing. Eur J Pain 2015;19:805–806.
38. Gerdle B, Ghafouri B, Ernberg M, Larsson B. Chronic musculoskeletal pain: Review of mechanisms and biochemical biomarkers as assessed by the microdialysis technique. J Pain Res 2014;7:313–326.
39. Clauw DJ. Fibromyalgia: Update on mechanisms and management. J Clin Rheumatol 2007;13:102–109.
40. King CD, Wong F, Currie T, Mauderli AP, Fillingim RB, Riley JL 3rd. Deficiency in endogenous modulation of prolonged heat pain in patients with irritable bowel syndrome and temporomandibular disorder. Pain 2009;143:172–178.
41. Oono Y, Wang K, Baad-Hansen L, et al. Conditioned pain modulation in temporomandibular disorders (TMD) pain patients. Exp Brain Res 2014;232:3111–3119.
42. Kothari SF, Baad-Hansen L, Oono Y, Svensson P. Somatosensory assessment and conditioned pain modulation in temporomandibular disorders pain patients. Pain 2015;156:2545–2555.
43. Lanefelt SV, Mélo-Gómez M, Chizari M, et al. Tooth clenching until exhaustion evokes exercise-induced hypoalgesia in healthy persons and in patients with temporomandibular disorders. J Oral Facial Pain Headache 2018 [epub ahead of print Aug 20].
44. Moana-Filho EJ, Herrero Babiloni A, Theis-Mahon NR. Endogenous pain modulation in chronic orofacial pain: A systematic review and meta-analysis. Pain 2018;159:1441–1455.
45. Dailey DL, Keffala VJ, Sluka KA. Do cognitive and physical fatigue tasks enhance pain, cognitive fatigue, and physical fatigue in people with fibromyalgia? Arthritis Care Res (Hoboken) 2015;67:288–296.
46. Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. Pain 2005;118:176–184.
47. Bement MK, Sluka KA. Low-intensity exercise reverses chronic muscle pain in the rat in a naloxone-dependent manner. Arch Phys Med Rehabil 2005;86:1736–1740.
48. INfORM. RDC-TMD. http://www.rdc-tmdinternational.org/TMDAssessmentDiagnosis/RDC-TMD.aspx. Accessed 19 November, 2018.
49. Spitzer RL, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: The GAD-7. Arch Intern Med 2006;166:1092–1097.
50. Ohrbach R, Larsson P, List T. The jaw functional limitation scale: Development, reliability, and validity of 8-item and 20-item versions. J Orofac Pain 2008;22:219–230.
51. Ohrbach R, Fillingim RB, Mulkey F, et al. Clinical findings and pain symptoms as potential risk factors for chronic TMD: Descriptive data and empirically identified domains from the OPPERA case-control study. J Pain 2011;12(11 suppl):T27–T45.
52. Ohrbach R, Knibbe W. Scoring Manual for Self-Report Instruments. In: Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), 2016:17.
53. Nasri-Heir C, Khan J, Benoliel R, et al. Altered pain modulation in patients with persistent postendodontic pain. Pain 2015; 156:2032–2041.
54. Yarnitsky D, Granot M, Nahman-Averbuch H, Khamaisi M, Granovsky Y. Conditioned pain modulation predicts duloxetine efficacy in painful diabetic neuropathy. Pain 2012;153:1193–1198.
55. Boonstra AM, Schiphorst Preuper HR, Balk GA, Stewart RE. Cut-off points for mild, moderate, and severe pain on the visual analogue scale for pain in patients with chronic musculoskeletal pain. Pain 2014;155:2545–2550.
56. Gracely R. Studies of pain in human subjects. In: McMahon SB, Koltzenburg M (eds). Wall and Melzack's Textbook of Pain, ed 5. Philadelphia: Elsevier/Churchill Livingstone, 2006:267–289.

57. de Leeuw R, Klasser GD, American Academy of Orofacial Pain. Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management, ed 6. Chicago: Quintessence, 2018.
58. Raphael KG, Janal MN, Anathan S, Cook DB, Staud R. Temporal summation of heat pain in temporomandibular disorder patients. J Orofac Pain 2009;23:54–64.
59. Zhang Y, Shao S, Zhang J, Wang L, Wang K, Svensson P. Temporal summation and motor function modulation during repeated jaw movements in patients with temporomandibular disorder pain and healthy controls. Pain 2017;158:1272–1279.
60. Khan J, Benavent V, Korczeniewska OA, Benoliel R, Eliav E. Exercise-induced hypoalgesia profile in rats predicts neuropathic pain intensity induced by sciatic nerve constriction injury. J Pain 2014;15:1179–1189.
61. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. Pain 1996;64:415–423.
62. Vierck CJ Jr, Staud R, Price DD, Cannon RL, Mauderli AP, Martin AD. The effect of maximal exercise on temporal summation of second pain (windup) in patients with fibromyalgia syndrome. J Pain 2001;2:334–344.
63. Lannersten L, Kosek E. Dysfunction of endogenous pain inhibition during exercise with painful muscles in patients with shoulder myalgia and fibromyalgia. Pain 2010;151:77–86.
64. Dietrich A, McDaniel WF. Endocannabinoids and exercise. Br J Sports Med 2004;38:536–541.
65. Droste C, Meyer-Blankenburg H, Greenlee MW, Roskamm H. Effect of physical exercise on pain thresholds and plasma beta-endorphins in patients with silent and symptomatic myocardial ischaemia. Eur Heart J 1988;9(suppl N):s25–s33.
66. Koltyn KF, Brellenthin AG, Cook DB, Sehgal N, Hillard C. Mechanisms of exercise-induced hypoalgesia. J Pain 2014;15:1294–1304.
67. Chalaye P, Lafrenaye S, Goffaux P, Marchand S. The role of cardiovascular activity in fibromyalgia and conditioned pain modulation. Pain 2014;155:1064–1069.
68. Ring C, Edwards L, Kavussanu M. Effects of isometric exercise on pain are mediated by blood pressure. Biol Psychol 2008;78:123–128.
69. Zamir N, Maixner W. The relationship between cardiovascular and pain regulatory systems. Ann N Y Acad Sci 1986;467:371–384.
70. Lemley KJ, Hunter SK, Bement MK. Conditioned pain modulation predicts exercise-induced hypoalgesia in healthy adults. Med Sci Sports Exerc 2015;47:176–184.
71. Stolzman S, Bement MH. Does exercise decrease pain via conditioned pain modulation in adolescents? Pediatr Phys Ther 2016;28:470–473.
72. Geva N, Defrin R. Enhanced pain modulation among triathletes: A possible explanation for their exceptional capabilities. Pain 2013;154:2317–2323.
73. Vaegter HB, Handberg G, Graven-Nielsen T. Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans. Pain 2014;155:158–167.
74. Goldenberg DL, Burckhardt C, Crofford L. Management of fibromyalgia syndrome. JAMA 2004;292:2388–2395.
75. Ageberg E, Link A, Roos EM. Feasibility of neuromuscular training in patients with severe hip or knee OA: The individualized goal-based NEMEX-TJR training program. BMC Musculoskelet Disord 2010;11:126.
76. Hurkmans E, van der Giesen FJ, Vliet Vlieland TP, Schoones J, Van den Ende EC. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. Cochrane Database Syst Rev 2009;(4):CD006853.
77. Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue syndrome. Pain 2004;109:497–499.
78. Hoffman MD, Shepanski MA, Ruble SB, Valic Z, Buckwalter JB, Clifford PS. Intensity and duration threshold for aerobic exercise-induced analgesia to pressure pain. Arch Phys Med Rehabil 2004;85:1183–1187.
79. Vaegter HB, Handberg G, Graven-Nielsen T. Isometric exercises reduce temporal summation of pressure pain in humans. Eur J Pain 2015;19:973–983.
80. Koltyn KF, Garvin AW, Gardiner RL, Nelson TF. Perception of pain following aerobic exercise. Med Sci Sports Exerc 1996;28:1418–1421.
81. Koltyn KF, Trine MR, Stegner AJ, Tobar DA. Effect of isometric exercise on pain perception and blood pressure in men and women. Med Sci Sports Exerc 2001;33:282–290.
82. Koltyn KF, Umeda M. Exercise, hypoalgesia and blood pressure. Sports Med 2006;36:207–214.
83. Ghione S, Rosa C, Panattoni E, Nuti M, Mezzasalma L, Giuliano G. Comparison of sensory and pain threshold in tooth pulp stimulation in normotensive man and essential hypertension. J Hypertens Suppl 1985;3:s113–s115.
84. Ghione S. Hypertension-associated hypalgesia. Evidence in experimental animals and humans, pathophysiological mechanisms, and potential clinical consequences. Hypertension 1996;28:494–504.
85. Schobel HP, Handwerker HO, Schmieder RE, Heusser K, Dominiak P, Luft FC. Effects of naloxone on hemodynamic and sympathetic nerve responses to pain in normotensive vs borderline hypertensive men. J Auton Nerv Syst 1998;69:49–55.
86. Umeda M, Newcomb LW, Koltyn KF. Influence of blood pressure elevations by isometric exercise on pain perception in women. Int J Psychophysiol 2009;74:45–52.
87. Umeda M, Newcomb LW, Ellingson LD, Koltyn KF. Examination of the dose-response relationship between pain perception and blood pressure elevations induced by isometric exercise in men and women. Biol Psychol 2010;85:90–96.
88. Carlson CR, Reid KI, Curran SL, et al. Psychological and physiological parameters of masticatory muscle pain. Pain 1998;76:297–307.
89. Stone AA, Broderick JE. Obesity and pain are associated in the United States. Obesity (Silver Spring) 2012;20:1491–1495.
90. Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: A comparison of diffuse noxious inhibitory controls in healthy older and younger adults. Pain 2003;101:155–165.
91. Grashorn W, Sprenger C, Forkmann K, Wrobel N, Bingel U. Age-dependent decline of endogenous pain control: Exploring the effect of expectation and depression. PLoS One 2013;8:e75629.
92. Bailey KM, Carleton RN, Vlaeyen JW, Asmundson GJ. Treatments addressing pain-related fear and anxiety in patients with chronic musculoskeletal pain: A preliminary review. Cogn Behav Ther 2010;39:46–63.
93. Krogstad BS, Jokstad A, Dahl BL, Vassend O. The reporting of pain, somatic complaints, and anxiety in a group of patients with TMD before and 2 years after treatment: Sex differences. J Orofac Pain 1996;10:263–269.
94. Tavares LM, da Silva Parente Macedo LC, Duarte CM, de Goffredo Filho GS, de Souza Tesch R. Cross-sectional study of anxiety symptoms and self-report of awake and sleep bruxism in female TMD patients. Cranio 2016;34:378–381.
95. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: A systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain 2012;28:819–841.
96. de Souza Moura AM, Lamego MK, Paes F, et al. Effects of aerobic exercise on anxiety disorders: A systematic review. CNS Neurol Disord Drug Targets 2015;14:1184–1193.
97. Kelley GA, Kelley KS, Callahan LF. Community-deliverable exercise and anxiety in adults with arthritis and other rheumatic diseases: A systematic review with meta-analysis of randomised controlled trials. BMJ Open 2018;8:e019138.
98. Morris L, Stander J, Ebrahim W, et al. Effect of exercise versus cognitive behavioural therapy or no intervention on anxiety, depression, fitness and quality of life in adults with previous methamphetamine dependency: A systematic review. Addict Sci Clin Pract 2018;13:4.