Experimental pain thresholds and psychosocial features across menstrual cycle in myofascial orofacial pain compared to healthy individuals: cross-sectional study

Limiares de dor experimental e características psicossociais ao longo do ciclo menstrual na dor miofascial orofacial em comparação com indivíduos saudáveis: estudo transversal

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ABSTRACT

BACKGROUND AND OBJECTIVES: The hormonal impact on pain perception during the menstrual cycle is a major focus of study, and further elucidation in temporomandibular disorders (TMD) field is necessary. Thus, this cross-sectional study evaluated experimental pain thresholds, psychosocial features, and clinical pain report on TMD women across menstrual cycle *versus* healthy controls.

METHODS: A total of 220 women's clinical files were screened, with 80 selected and divided into control group (healthy individuals, n=40) and TMD group (myofascial pain, n=40). Regarding the menstrual cycle phases, the files were divided into Pre-Luteal and Luteal. The Perceived Stress Scale (PSS), Pain Catastrophizing Scale (PCS), Mechanical Pain Threshold (MPT), Wind-up (WUR), Pressure Pain Threshold (PPT), Conditioned Pain Modulation (CPM) and Visual Analogue Scale (VAS) were analyzed at a 5% significance level, by Two-Way ANOVA test and *post hoc* Tukey test.

RESULTS: PSS and PCS were significantly different between TMD and control group (p<0.001), regardless of menstrual cycle. Healthy individuals in the Luteal phase presented higher MPT values compared to the other phases (p<0.001). PPT showed significant difference across menstrual phases (p=0.022), but no differences in multiple comparisons. VAS values showed no difference between menstrual cycle phases (p=0.376).

CONCLUSION: Finally, healthy individuals in the Luteal phase have higher MPT and PPT values on the orofacial region. Pain report in patients with TMD showed no difference throughout the menstrual cycle, showing that small alterations on experimental pain thresholds may not be clinically relevant. The presence of chronic pain seems to be more related to psychosocial features than hormonal fluctuations.

Keywords: Chronic pain, Gonadal hormones, Menstrual cycle, Pain threshold, Temporomandibular joint dysfunction syndrome.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O impacto do ciclo menstrual na percepção da dor é um foco importante de estudo, sendo necessária uma maior elucidação na disfunção temporomandibular (DTM). Assim, este estudo transversal avaliou limiares de dor experimental, características psicossociais e relatos de dor em mulheres com DTM ao longo do ciclo menstrual, comparadas com controles saudáveis.

MÉTODOS: 220 prontuários de mulheres foram analisados, sendo 80 selecionados para os grupos de controle (saudáveis, n=40) e DTM (dor miofascial, n=40). Nas fases do ciclo menstrual, as pacientes foram divididas nas categorias Pré-Luteal e Luteal. Os instrumentos Escala de Estresse Percebido (PSS), Escala de Pensamentos Catastróficos (PCS), Limiar de Dor Mecânica (MPT), *Wind-up Ratio* (WUR), Limiar de Dor à Pressão (PPT), Modulação Condicionada da Dor (CPM) e Escala analógica visual (EAV) foram analisados com nível de significância de 5%, pelos testes ANOVA de dois fatores e Tukey *post hoc*.

RESULTADOS: As escalas PSS e PCS foram significativamente diferentes entre os grupos DTM e controle (p<0,001), independentemente do ciclo menstrual. Indivíduos saudáveis na fase luteal apresentaram MPT maior em comparação com outras fases (p,0,001). O PPT mostrou diferença significativa entre as fases menstruais (p=0,022), sem diferença nas comparações múltiplas. Os valores da EAV não apresentaram diferença entre as fases menstruais (p=376).

CONCLUSÃO: Indivíduos saudáveis na fase luteal têm MPT e PPTl maior na região orofacial. Os relatos de dor em pacientes com DTM não mostraram diferença ao longo do ciclo mens-

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trual, indicando que pequenas alterações nos limiares experimentais podem ser clinicamente relevantes. A presença de dor crônica parece estar mais relacionada com características psicossociais do que com flutuações hormonais.
Descritores: Ciclo menstrual, Dor crônica, Hormônios gonodais, Limiar da dor, Síndrome da disfunção da articulação temporomandibular.

INTRODUCTION

Temporomandibular disorders (TMDs) are characterized by pain and/or function impairment of the temporomandibular joint (TMJ), masticatory muscles and/or associated structures[1-3]. Epidemiologic studies reveals that TMDs are more prevalent on women, who seek for pain treatment more frequently than men, likewise other musculoskeletal chronic conditions[2,4]. Due to the higher frequency of this conditions on women, many authors deduce and suggest the existence of a factor differentiating both sexes on pain maintenance and perception[4-8], related to hormones discrepancies[5,7-10].

Gonadal hormones present different levels on men and women, and evidences suggest an involvement of the hypothalamic-pituitary-gonadal axis (HPA)[4,8,11]. Estrogen and progesterone seem to present modulation effects on nociception, and its fluctuation across the menstrual cycle may lead to alterations on pain perception[9,10,12-14]. Also, mood and peripheral sensitization to external stimuli are proven to be modulated by estrogen and progesterone. This set of effects can affect pain thresholds and perception[1,7,9].

Therefore, the influence of sexual hormones and the menstrual cycle on pain behavior are not well established. Some authors did not found differences on pain thresholds across the menstrual cycle[15] and others did, but at divergent stages[1,16-20]. Due to discrepancies on methodologies and results found in scientific literature, more studies evaluating the role of these variables in pain would contribute to a better understanding on pain behavior and management. Thus, the aim of the present study was to evaluate experimental pain thresholds, psychosocial features, and clinical pain report on women with TMD diagnosis across the menstrual cycle in comparison to healthy individuals. The null hypothesis is that pain thresholds and psychosocial features do not vary across menstrual cycle, not resulting on pain facilitation.

METHODS

The present retrospective cross-sectional was conducted in accordance with the Declaration of Helsinki and the STROBE (The Strengthening the Reporting of Observational Studies in Epidemiology)[21] guidelines for cross-sectional studies (Approved by the Local Research Ethics Committee - Opinion Number 82201818.3.0000.5417).

Files comprising data collected in a dentistry school and an orofacial pain outpatient center, from October of 2018 to March of 2020, from a southwestern Brazilian population, were screened, resulting on 220 files. Those went to a thorough analysis according to inclusion/exclusion criteria.

Initial exclusion criteria were files without precise data on first day of menstrual cycle, patients under oral, injectable and/or intrauterine contraceptives or any hormonal reposition therapy. Furthermore, individuals with medical problems and/or neurological disorders were also excluded. The inclusion criteria comprised women between 18 to 49 years old with regular menstrual cycles, between 26 to 33 days, with no gynecologic disorders, who underwent examination according to Research Diagnostic Criteria for Temporomandibular Disorders (DC/TMD)[22]. Patients presenting masticatory muscular pain (temporalis or masseter) affected by jaw movement, function, or parafunction with eliciting or exacerbating pain upon muscular palpation were diagnosed with myalgia.

Regarding the presence of TMD, the patients were divided into two groups: TMD (myofascial pain diagnosis) and control (health individuals). In relation to the menstrual cycle phase, the patients were divided into two groups: Pre-luteal phase (when evaluated between the first and 14th day of the menstrual cycle) and luteal phase (when evaluated in or after 15th day of the cycle). The variables included in the analysis were the Brazilian validated Perceived Stress Scale (PSS) and Pain Catastrophizing Scale (PCS) questionnaires, Mechanical Pain Threshold (MPT), Wind-up Ratio (WUR), Pressure Pain Threshold (PPT) and Conditioned Pain Modulation (CPM) from the Quantitative Sensory Testing (QST) protocol[23], and the pain Visual Analog Scale (VAS), collected only from TMD group. All the variables included were collected by the same standardized protocol.

Perceived Stress Scale (PSS)

This questionnaire consisted of 14 items aimed to measure the degree of perceived stress in the last month considering the individual's global context and how unpredictable, uncontrollable, and overwhelmed the respondents assess their lives. The total score varied from zero to 56, based in the sum of the score for each item[24].

Pain Catastrophizing Scale (PCS)

This questionnaire measured catastrophic thoughts about pain, especially in severe pain phase, through the indication of the frequency the individuals have catastrophic thoughts about their pain. PCS is comprised of 13 statements of pain catastrophic thoughts with a frequency scale ranging from 0–5 (0 = hardly ever and 5 = almost always). The total score was calculated by adding up all the scored items and ranged from 0 to 52 points. The higher the value, the higher the degree of catastrophizing[25].

Sensory testing

This study evaluated three parameters of the QST battery for mechanical somatosensory assessment on the dominant side for control group (masseter insertion region), and on the side where the patient reported more severe pain during clinical examination for TMD group. The QST battery consisted of: (a) MPT, (b) WUR, and (c) PPT.

Mechanical Pain Threshold (MPT)

MPT test consists of using monofilaments adapted by Semmes-Weinstein to determine the Mechanical Pain Threshold. The kit contains 20 nylon Von Frey monofilaments of different diameters calibrated to exert specific forces, varying from 0.008 to 300 g/mm^2, increasing as the monofilament caliber also increases. Each monofilament was applied perpendicularly to the region to be evaluated and light pressure was applied until the filament bended. The participant was instructed to report verbally when he felt a "prick, pinprick, or slightly painful sting" sensation in the contact area of the monofilaments.

The tests started with a smaller caliber filament (0.008 g/mm^2) that was sequentially increased until the volunteer verbally reported feeling a slightly painful needle stick, as previously instructed. This was considered a positive stimulus. A negative stimulus was also sought. With a reversed order, a lower caliber filament was applied until the volunteer no longer felt the application of the harmful tactile stimulus (touch and not a painful needle stick). Five negative stimuli (descending) and five positive stimuli (ascending) were obtained, and a geometric mean of these repetitions was calculated[23,26].

Wind-up Ratio (WUR)

The test was performed with the smallest Von Frey filament that caused a sensation of mild pain. The chosen filament was placed on the skin over the region of the masseter muscle and pressure was applied until the filament bended. This test was performed in a continuous sequence where the intensity of a single painful stimulus with the filament was compared with that of a series of 10 consecutive stimuli with the same filament and with the same intensity of force (1 per second applied within a 1 cm^2 area). This sequence was repeated three times and the pain intensity values from zero (no pain) to 100 (worst pain) were quantified using a Numerical Rating Scale (NRS) at two moments: (1) after the single stimulus and (2) at the end of the series of 10 consecutive stimuli. The WUR was calculated by the reason for the temporal sum of pain, dividing the average pain intensity reported in the series of 10 consecutive stimuli by the average pain intensity reported during the single stimuli[23,26].

Pressure Pain Threshold (PPT)

PPT measurements were performed using a pressure algometer, with a flat circular tip of 1 cm^2, through which a constant and increasing pressure of approximately 0.5 kg/cm^2/s was applied. Prior to the examination, individuals were trained to press the button that registers the force applied by the device when the sensation of pressure turns into a slightly painful stimulus (pressure pain threshold). Three measurements were obtained in the sequence and the arithmetic mean was considered as the PPT value[23,26].

Conditioned Pain Modulation (CPM)

A CPM-sequential paradigm was performed. After measuring the PPT, as explained above, the individual was instructed to immediately immerse the contralateral hand (in relation to the PPT test site) in a water-cooled container for a maximum of 1 min. In the case of TMD group, it was the hand on the side with the least pain. Previously to the test, the participant was instructed to report the intensity of pain on a NRS immediately after the hand was immersed in the water in a certain temperature that was decreasing. When the individual reported pain intensity ≥ 03 on the NRS, the temperature was considered the temperature for the test. Through this parameter, the temperature varied between 10°C and 16°C among the participants. The first PPT was considered the test stimulus (TS) and the immersion of the hand in water-cooled was the conditioning stimulus (CS). Thus, the CPM value was calculated as the absolute difference between "TS and CS"[27].

Visual Analog Scale (VAS)

VAS was filled out by the TMD group participants. The scale consisted of a horizontal 10 cm line between the phrases: "no pain at all" and "the worst pain I have ever felt" and required patients to draw a mark on the line to indicate their pain intensity at the moment of the evaluation before clinical tests[28].

Statistical analysis

Statistical analyses were conducted on the open-source Jamovi software 2.23.6 (Sydney, Australia), with a significance level of 5%. After Shapiro-Wilk test for normality distribution, the variables (Age, PCS, MPT, PPT, WUR, CPM and VAS) did not present a normal distribution and were adapted through a logarithmic transformation for ANOVA tests. The one-way ANOVA test was applied for age comparison between TMD and control groups and for VAS values comparison among the menstrual cycle phases. The Two-Way ANOVA test was performed to compare the menstrual cycle phase to the evaluated variables. When the comparison was statistically significant ($p<0.05$), the *post-hoc* Tukey test was used to check the interactions.

RESULTS

After the analysis according to the inclusion/exclusion criteria, the sample comprised 80 files (Figure 1) from women ranging from 20 to 49 years old. The control group presented a mean age of 32.35 ± 7.45 years-old and the TMD group of 33.17 ± 9.0 years-old, without statistically significant difference between groups ($p=0.617$). The TMD group reported a mean VAS pain value of 4.8 ± 3.3 and median of 36 months (interquartile range = 54 months) of pain.

Table 1 shows the mean values of all variables collected on both control and TMD groups and the different menstrual cycle phases. Table 2 evidences the comparison between control and TMD groups values through different menstrual cycles phases, and its interactions with each of the subgroups. PSS ($p=0.001$) and PCS ($p<0.001$) showed significant higher values on TMD group when compared to healthy controls. MPT presented higher mean values on control group ($p=0.033$) and Luteal phase ($p<0.001$). When interactions were checked on the subgroups, the Luteal phase from control group (2) had higher means when compared to all other subgroups ($p<0.001$). VAS scores values compared at different menstrual cycle phases in TMD group are shown in Table 3, where no differences were found ($p=0.376$).

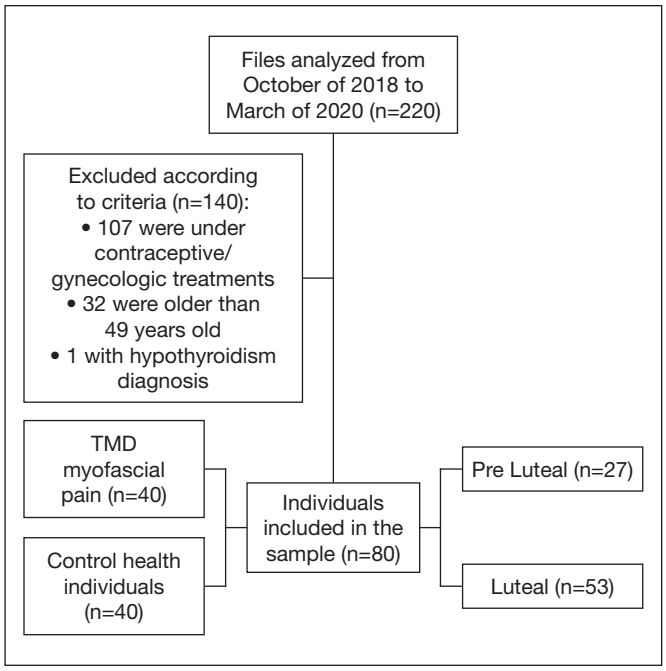

Figure 1. Eligibility flowchart

Table 3. One-way ANOVA VAS comparison between both menstrual cycle phases in TMD group.

TMD (n=40)	VAS (cm)
Pre-luteal (n=14)	4.40 ± 3.25
Luteal (n=26)	5.39 ± 3.35
p-value	p=0.376[1]

[1]One-way ANOVA; p<0.05; TMD group = masticatory myofascial pain; VAS = Visual Analog Scale.

DISCUSSION

The present study's objective was to evaluate experimental pain thresholds, psychosocial features, and clinical pain report on women with TMD diagnosis across the menstrual cycle phases. The results showed that: 1) PSS and PCS presented with higher values on TMD patients independent of menstrual cycle phase; 2) Luteal control patients showed higher values on MPT; and 3) Pain VAS scores did not differ between menstrual cycle phases on TMD patients. The null hypothesis was rejected regarding psychosocial variables and experimental pain, in accordance with the findings previously mentioned.

Table 1. Mean values ± standard deviation of the variables collected divided into menstrual cycle phases in the groups.

	PSS	PCS	MPT (g/mm^2)	WUR (g/mm^2)	PPT (Kgf/cm^2)	CPM
Control (n=40)	23.4 ± 6.93	15.4 ± 10.6	91.0 ± 113.0	1.81 ± 0.822	1.74 ± 0.913	0.036 ± 0.489
Pre-luteal (n=13) (1)	22.2 ± 7.87	16.9 ± 11.3	15.5 ± 35.9	1.69 ± 0.789	1.22 ± 0.513	0.142 ± 0.538
Luteal (n=27) (2)	23.9 ± 6.52	16.9 ± 10.1	127.0 ± 119.0	1.86 ± 0.846	1.98 ± 0.965	-0.014 ± 0.467
TMD (n=40)	29.6 ± 9.00	27.1 ± 12.80	47.7 ± 93.1	1.96 ± 0.992	1.67 ± 0.900	-0.060 ± 0.539
Pre-luteal (n=14) (3)	29.7 ± 9.38	28.0 ± 12.9	51.5 ± 103.0	1.93 ± 1.09	1.67 ± 0.783	-0.098 ± 0.472
Luteal (n=26) (4)	29.4 ± 8.59	25.5 ± 12.9	40.6 ± 73.5	2.00 ± 0.806	1.66 ± 1.12	0.010 ± 0.660

PSS = Perceived Stress Scale; PCS = Pain Catastrophizing Thoughts Scale; MPT = Mechanical Pain Threshold; WUR = Wind-up Ratio; PPT = Pressure Pain Threshold; CPM = Conditioned Pain Modulation; TMD group = masticatory myofascial pain; (1) Pre-luteal control; (2) Luteal control; (3) Pre-luteal TMD; (4) Luteal TMD.

Table 2. Two-Way ANOVA test and Tukey *post-hoc* interactions results on collected variables.

	PSS[1]		PCS[1]		MPT[1]		WUR[1]		PPT[1]		CPM[1]	
Control (1; 2) x tmd (3; 4)	F=11.33	**p=0.001**	F=142.31	**p<0.001**	F=4.71	**p=0.033**	F=1.08	p=0.301	F=1.68	p=0.198	F=0.123	p=0.727
Pre-luteal (1) (3) x luteal (2) (4)	F=0.14	p=0.702	F=0.27	p=0.602	F=15.35	**p<0.001**	F=0.79	p=0.374	F=0.473	p=0.494	F=0.370	p=0.370
tmd/control x cycle phases	F=0.29	p=0.592	F=0.40	p=0.527	F=12.62	**p<0.001**	F=0.22	p=0.638	F=5.43	**p=0.022**	F=0.537	p=0.537
Interactions[2]												
1x2	N/A		N/A		**p<0.001**		N/A		p=0.157		N/A	
1x3	N/A		N/A		p=0.771		N/A		p=0.889		N/A	
1x4	N/A		N/A		p=0.706		N/A		p=0.982		N/A	
2x3	N/A		N/A		**p<0.001**		N/A		p=0.326		N/A	
2x4	N/A		N/A		**p<0.001**		N/A		p=0.052		N/A	
3x4	N/A		N/A		p=0.994		N/A		p=0.646		N/A	

[1]Two-way ANOVA test; [2]Tukey test; **p<0.05**; PSS = Perceived Stress Scale; PCS = Pain Catastrophizing Thoughts Scale; MPT = Mechanical Pain Threshold; WUR = Wind-up Ratio; PPT = Pressure Pain Threshold; CPM = Conditioned Pain Modulation; TMD group = masticatory myofascial pain; (1) Pre-luteal control; (2) Luteal control; (3) Pre-luteal TMD; (4) Luteal TMD.

There is a consensus about the fluctuations of sexual hormones during the menstrual phases[9,14,29], leading to a massive search for a relation with pain prevalence on women[5,10,20,30,31]. These hormones fluctuations are also associated with higher variabilities on women's mood, that indirectly influences on pain, once symptoms of stress and anxiety are present on normal cycling women, frequently around the perimenstrual moment[10,13], when lower estrogen/progesterone levels are noticed and probably related to an increase on sympathetic activation and decrease on cognitive pain modulation, highly associated with stress, anxiety and pain facilitation[13,32]. Stress and catastrophizing thoughts, e.g., are also strongly presented in women with chronic pain, leading to an exacerbation of pain[2,7,33].

The present study evaluated outcomes associated with menstrual cycle phases and found higher values of stress and catastrophizing thoughts (PSS and PCS questionnaires) on the TMD group compared to the control group, independently of the menstrual cycle phases. Hence, presence of chronic pain seems to be more related to psychosocial features than hormonal fluctuation itself.

As mentioned before, estrogen/progesterone serum levels may be related to different pain perception on experimental orofacial pain[1,3,6,8,15-18,20,31,34]. As an example, the occurrence of pathological dysfunctions within the hypothalamic-pituitary-adrenal (HPA) axis, characterized by reductions in circulating levels of estrogen and progesterone, has been observed to be associated with increased frequencies of TMD) in female patients[35]. In the present study, parameters as MPT, WUR, PPT and CPM were accessed, but only MPT ($p<0.001$) and PPT ($p=0.022$) showed significant differences between menstrual cycle phases. Luteal control patients presented higher thresholds on MPT when compared to all phases on both control and TMD groups ($p<0.001$).

Luteal phase is characterized by predominant moments of high estrogen/progesterone levels with less steeply declining events when compared to pre-luteal phase, especially on its early period, in which these levels are at a very low point[4,9,10]. Estrogen and progesterone have peripheral and central receptors indicating its action on different pain mechanisms[4], which are fundamental for its initiation and its maintenance.

On peripheral and acute events, high estrogen/progesterone levels are closely related to a pronociceptive behavior through glutaminergic pathways and nerve growth factor (NGF) modulation, leading to hyperalgesia and allodynia[10,36,37]. Otherwise, on central nervous system, high estrogen/progesterone levels are related to an increase on endogenous inhibitory pain modulation through activation of serotonergic, GABAergic and opioid pathways[9,10,13].

Due to the median time of pain reported in this study's sample (36 months) characterizing probable chronic patients, it is possible to infer that the high estrogen/progesterone levels showed more activity on pain inhibition by central mechanisms than pronociceptive events. Thus, the probable absence of central sensitization and lack of long exposure to pain events on control group patients may be a key factor for the enhanced hormone-induced antinociception. The higher PPT values on Luteal phase of control patients corroborates with the previous findings.

Although experimental pain showed differences across the menstrual cycle phases, VAS pain scores in the present study were not statistical different between menstrual cycle phases on TDM group ($p=0.376$), in agreement with previous studies[17,19]. These data evidence that minor alterations on experimental pain tests may not be clinically relevant or represent a daily routine on patient's pain report.

The present study performed controlled and efficient tests on experimental pain, also blinded the main study focus from patients and included psychosocial variables that may interfere with pain perception[9]. The limitations of the present study comprise a small convenience sample, evaluated on a one-time cross-sectional method, with no daily control on hormone levels and menstrual cycle phases by gold standard and recommended method (blood or urine samples). Despite the wide range of studies involving TMD and menstrual cycle phases available in the literature, the lack of standardized methodologies make it hard to compare the present findings with other studies.

CONCLUSION

Individuals without any chronic pain condition on Luteal phase of the menstrual cycle tend to have higher MPT and PPT thresholds on orofacial region, although the pain report on myofascial pain patients was not significantly different across menstrual cycle phases, elucidating that minor alterations on experimental pain thresholds may be not clinically relevant. Lastly, the presence of chronic pain seems to be more related to psychosocial features than hormonal fluctuation itself.

AUTHORS' CONTRIBUTIONS

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Statistical Analysis, Research, Methodology, Writing - Review and Editing
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