Systemic diseases and other painful conditions in patients with temporomandibular disorders and migraine

Edwin Fernando Ruiz CONTRERAS[a]
Giovana FERNANDES[b]
Paula Cristina Jordani ONGARO[b]
Leticia Bueno CAMPI[b]
Daniela Aparecida Godoi GONÇALVES[b]

[a]Universidade Estadual de Londrina – UEL, Department of Restorative Dentistry, Londrina, PR, Brazil.

[b]Universidade Estadual Paulista – UNESP, Araraquara Dental School, Department of Dental Materials and Prosthodontics, Araraquara, SP, Brazil.

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Corresponding Author:
Edwin Fernando Ruiz Contreras
E-mail: edwinfrc@gmail.com

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Abstract: Temporomandibular disorders (TMD) are a highly prevalent, painful musculoskeletal condition affecting the masticatory system, and are frequently associated with migraines (M) and other diseases. This study aimed to investigate the association between painful TMD and M with other painful conditions and systemic diseases, such as cervicalgia, body pain (BP), ear-nose-throat disorders, musculoskeletal disorders, diabetes, cardiopulmonary diseases and gastritis/peptic ulcer. Methods: This was a cross-sectional study conducted in a sample of 352 individuals. Participants were stratified into three groups according to the presence of painful TMD and M: controls [individuals free of TMD and any headache (HA)]; TMD only (presence of painful TMD, but free of any HA); and TMD+M (presence of painful TMD and M). TMD was classified according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) - Axis I. Nonspecific physical symptoms (NSPS) were assessed by RDC/TMD - Axis II. The International Classification of Headache Disorders - II criteria, second edition, were applied to identify and classify primary HA. Other painful conditions and systemic diseases were assessed by volunteers' self-report. The prevalence of all assessed conditions was higher in the TMD+M group. Multiple regression models showed that cervicalgia was associated with the TMD only group ($p<0.05$), whereas gender ($p<0.05$), cervicalgia ($p<0.05$), BP ($p<0.05$) and NSPS ($p<0.05$) were significantly associated with the TMD+M group. Our results suggest that individuals with a comorbidity (TMD associated with M) have a more severe condition than those presenting only painful TMD.

Keywords: Migraine Disorders; Temporomandibular Joint Disorders; Neck Pain; Headache; Comorbidity.

Introduction

Temporomandibular disorders (TMD) are considered a type of functional pain syndrome (FPS) or idiopathic pain disorder (IPD), which also include conditions such as fibromyalgia, low back pain, irritable bowel syndrome, chronic headaches (HA), interstitial cystitis, chronic pelvic pain, chronic tinnitus, whiplash-associated

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disorders, and vulvar vestibulitis.[1] Whereas TMD is defined as a group of disorders involving the masticatory muscles, the temporomandibular joint (TMJ) and associated structures,[2] FPS, in general, is characterized by high levels of psychological distress (anxiety, health-seeking behavior and markers of somatization) and abnormalities in motor function, autonomic balance and sleep.[1,3] Although these disorders frequently occur concomitantly, the relationship among them remains unclear.[3] Moreover, FPS typically does not respond well to conventional therapies, indicating that a better understanding of its etiology and mechanism should be highly relevant to the medical field.[1]

A large proportion of patients with painful TMD also present a significant disability, with consequences that impact their lives. The simultaneous presence of pain in other body areas seems to increase the magnitude of the impact. Moreover, it has been demonstrated that painful TMD is strongly associated with other painful conditions,[4] such as fibromyalgia,[5,6] widespread pain,[5,6] cervical spine dysfunction,[7] neck pain, low back and joint pain[8] and primary HA.[9,10,11,12]

Among the comorbid conditions, some primary HA are more frequently associated with painful TMD.[9,10,13,14,15,16] The magnitude of the association is higher for migraine (M), followed by tension-type headaches (TTH).[10,11,12,13,14,15,16,17] Previous evidence has indicated that TMD is comorbid with M and a risk factor for M chronification.[9,11,12,13] Additionally, it has been demonstrated that the presence of a comorbidity negatively influences diagnostic tests for musculoskeletal pain.[18]

Although previous studies have shown an association between TMD and other painful conditions,[18,19] somatization, depression[5,18] and a reduced quality of life,[20] there is still a lack of information regarding the relationship between painful TMD (isolated or associated with M) and systemic diseases. Therefore, this study aimed to investigate the association between painful TMD and M with other painful conditions [such as cervicalgia, body pain (BP), musculoskeletal disorders (MED)] and systemic diseases [such as ear-nose-throat disorders (ENT), diabetes, cardiopulmonary diseases and gastritis/peptic ulcer]. We hypothesized that painful TMD was significantly associated with systemic diseases, and that the magnitude of the association would be greater in the case of painful TMD and M comorbidity, thus resulting in a higher burden of the disease.

Methods

Our sample was composed of 352 individuals. Of these, 305 were patients who sought care at the UNESP/Araraquara School of Dentistry, presenting with the chief complaint of orofacial pain, and 47 individuals (control group) were free of TMD, HA or any type of facial pain. The controls were selected among the patients seeking routine dental care treatment at the same university, or companions of patients. This group is relatively small, since finding individuals free of HA and TMD is not a simple task. We included individuals of both genders, aged between 18 and 65 years, presenting adequate bilateral occlusal contacts, and able to read and write. Exclusion criterion was the presence of any cognitive or communication impairment. The Research Ethics Committee of the Araraquara Dental School (UNESP - Universidade Estadual Paulista, Brazil), approved this study. Informed consent was obtained from each participant.

Assessments

Temporomandibular disorders and non-specific physical symptoms

Two trained researchers evaluated all the individuals, following a standardized orofacial pain clinic protocol, including an interview and a clinical exam. The chief complaint, characteristics of the pain (quality, duration, frequency, intensity, location, and exacerbating and alleviating factors), medical history and medication use were assessed. The TMD diagnosis and classification were made according to the diagnostic criteria of the American Academy of Orofacial Pain (AAOP)[2] and the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) - Axis I – Portuguese version, respectively.[22] The RDC/TMD – Axis I allowed us to confirm the diagnosis of TMD and

define its classification into muscle disorders (Group I), articular disorders (Group II and III), or both. Data analysis was performed by grouping the individuals according to the diagnosis of painful types of TMD, including those of muscular and/or articular origin. The nonspecific physical symptoms (NSPS) were assessed by the RDC/TMD - Axis II, item 2.3. According to this instrument, individuals were classified into two groups, those presenting or not presenting NSPS.

Painful conditions and systemic diseases

The presence of persistent painful conditions and systemic diseases in the last 6 months were assessed through the individuals' report during the interview. We assessed the presence of cervicalgia, BP, musculoskeletal disorders (arthritis, fibromyalgia, back pain), ENT (otitis, sinusitis, rhinitis), diabetes, cardiorespiratory conditions (hypertension, heart disease, asthma, bronchitis), and gastritis/peptic ulcer.

Migraine

Migraine was clinically diagnosed by a researcher with specific training in HA medicine, using a structured questionnaire based on the International Classification for Headache Disorders, second edition (ICHD-II).[23] The questions collected information regarding HA features (frequency and duration of episodes, laterality, characteristics of pain, exacerbation with movement), and associated symptoms (aura, nausea, photophobia, phonophobia, autonomic symptoms). This questionnaire has been used in performing epidemiological and clinical research in Brazil,[9,10,11,12,13] and can identify the existence of M, TTH, or primary HA. Only individuals free of any HA or presenting M were included in the sample.

Data Analysis

The presence of painful TMD only or TMD associated with M comprised the outcome variables. Gender, self-reported diseases, other painful conditions and presence of NSPS were considered predictor variables. The sample was stratified into three groups, according to the presence of painful TMD and M: control (free of TMD and any HA); TMD only group (individuals presenting painful TMD but free of any HA); TMD+M group (individuals presenting painful TMD and M).

Descriptive statistics and frequency counts were used to characterize the sample. Two logistic regression models were performed to investigate the association between the outcome variables. The first model was built to study what predictor variables were associated with the TMD only group, compared with the control group. The second model was performed to analyze what predictor variables were associated with the simultaneous presence of painful TMD and M (TMD+M group), compared with the control group. In both models, the variables showing significant association ($p < 0.05$) with the univariate analyses were included in the multiple logistic models. In the logistic regression model, the predictor variables with the weakest association to the outcome variable were removed. This procedure was repeated using a backward stepwise approach until all the variables retained in the model yielded $p < 0.05$. The p-to-exit is reported for each predictor variable removed. The data were checked for multicollinearity, using a tolerance value < 0.10 and a variance inflation factor > 10. All analyses were performed with the Statistical Package for the Social Sciences (SPSS) software, version 21.0 for Mac.

Results

Sample characterization

Initially, 507 volunteers were screened according to the protocol mentioned above. Of these, we excluded 93 individuals presenting other types of HA (no M), 21 presenting non-painful TMD, and 41 because of missing data regarding other diseases. The final sample consisted of 352 individuals stratified into three groups according to the presence of painful TMD and M (Figure). The descriptive data of the predictor variables stratified according to the three groups are shown in Table 1.

The majority of the sample were women (83.8%) ($p < 0.001$). Overall, the mean age was 37.7 ± 12.7, with no statistical difference among the groups

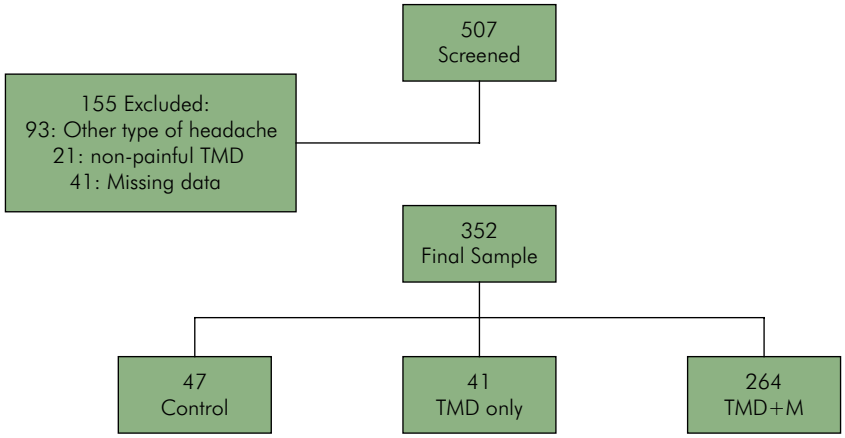

Figure 1. Participants flow diagram.

Table 1. Descriptive data of the predictor variables stratified according to the three groups.

Variable	Control	TMD only	TMD+M	Total
	47 (13.4)	41 (11.6)	264 (75)	352
Cervicalgia				
no	42 (38.5)	17 (15.6)	50 (45.9)	109 (100)
yes	5 (2.1)	23 (9.6)	212 (88.3)	240 (100)
Body Pain				
no	43 (23)	23 (12.3)	121 (64.7)	187 (100)
yes	4 (2.5)	17 (10.4)	142 (87.1)	163 (100)
MED				
no	32 (16.8)	23 (12.1)	135 (71.7)	190 (100)
yes	15 (9.3)	18 (11.1)	129 (79.6)	162 (100)
ENT				
no	31 (17.8)	20 (11.5)	123 (70.7)	174 (100)
yes	16 (9)	21 (11.8)	141 (79.2)	178 (100)
Diabetes				
no	44 (13.1)	36 (10.7)	255 (76.1)	335 (100)
yes	3 (17.6)	5 (29.4)	9 (52.9)	17 (100)
Cardiopulmonary				
no	39 (14.8)	31 (11.7)	194 (73.5)	264 (100)
yes	8 (9.1)	10 (11.4)	70 (79.5)	88 (100)
Gastritis/Peptic Ulcer				
no	41 (16.4)	28 (11.2)	181 (72.5)	250 (100)
yes	6 (5.9)	13 (12.7)	83 (81.4)	102 (100)
NSPS				
no	34 (43)	19 (24.1)	26 (32.9)	79 (100)
yes	13 (4.8)	22 (8.1)	238 (87.2)	273 (100)

TMD: Temporomandibular disorders; M: Migraine; MED: Musculoskeletal disorders; ENT: Ear, nose and throat disorders; NSPS: Non-specific physical symptoms.

($p > 0.05$); 47 (13.4%) participants had no TMD or HA, and 305 (86.6%) presented painful TMD. Among the individuals with painful TMD, 264 also presented M. The prevalence of each painful condition and systemic disease, according to the three groups, are presented in Table 2. The prevalence of painful conditions, systemic diseases and NSPS was higher among individuals with painful TMD associated with M (TMD + M group), compared with the controls and the individuals presenting only painful TMD (TMD only group).

The univariate analysis of the first regression model (TMD only compared with the control) showed that gender ($p = 0.036$), cervicalgia ($p < 0.001$), BP ($p = 0.001$), gastritis/peptic ulcer ($p < 0.05$) and NSPS ($p < 0.05$) were associated with the presence of painful TMD (Table 3). The multivariate analysis showed that the strongest predictor variable associated with the presence of TMD only was cervicalgia [odds ratio (OR): 10.0, 95%CI = 3.2–31.30].

In the second model (Table 4) (TMD+M vs. control), the univariate analyses indicated that gender ($p < 0.001$), cervicalgia ($p < 0.001$), BP ($p < 0.001$), MED ($p = 0.034$), ENT ($p = 0.016$), gastritis/peptic ulcer ($p = 0.012$) and NSPS ($p < 0.001$) were significantly associated with the presence of concomitant painful TMD and M. Multivariate analyses, in turn, showed that comorbidity (TMD+M group) was significantly associated with a wide

Table 2. Single and multiple logistic regression models for prediction of TMD only group versus the control group. The number of cases (n) included in the analysis is shown for each factor included in the single regression.

Predictor variables	n	Single regression			p -to-exit	Multiple regression		
		p-value	OR	95%CI		p-value	OR	95%CI
Gender								
Men	34	-	-	-	-	-	-	-
Women	54	0.036	2.6	1.07–6.41	0.163	-	-	-
Cervicalgia								
No	59	-	-	-	-	-	-	-
Yes	28	0.000	11.3	3.71–34.81	-	0.000	10.0	3.24–31.30
Body Pain								
No	66	-	-	-	-	-	-	-
Yes	21	0.001	7.9	2.39–26.41	0.340	-	-	-
MED								
No	55	-	-	-	-	-	-	-
Yes	33	0.248	1.7	0.70–3.98	-	-	-	-
ENT								
No	51	-	-	-	-	-	-	-
Yes	37	0.105	2.0	0.86–4.81	-	-	-	-
Diabetes								
No	80	-	-	-	-	-	-	-
Yes	8	0.352	2.0	0.46–9.11	-	-	-	-
Cardiorespiratory conditions								
No	70	-	-	-	-	-	-	-
Yes	18	0.395	1.6	0.55–4.46	-	-	-	-
Gastritis/Ulcer								
No	69	-	-	-	-	-	-	-
Yes	19	0.036	3.2	1.08–9.34	0.312	-	-	-
NSPS								
No	53	-	-	-	-	-	-	-
Yes	35	0.014	3.0	1.25–7.35	0.471	-	-	-

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variety of predictor variables, including gender [OR: 6.4 (95%CI = 2.38–16.99)], cervicalgia [OR: 10.0 (95%CI = 3.24–31.30)], BP [OR: 3.8 (95%CI = 1.06–13.53)], and NSPS [OR: 7.1 (95%CI = 2.81–18.06)].

Finally, the last model compared the TMD only group with the TMD+M group (Table 5). According to the univariate analyses, gender (p = 0.001), cervicalgia (p = 0.001), diabetes (p = 0.019) and NSPS (p < 0.001) were significantly associated with individuals presenting the concomitant presence of painful TMD and M, compared with those presenting only painful TMD. Multivariate analysis

Table 3. Single and multiple logistic regression models for prediction of the TMD+M versus the control group. The number of cases (n) included in the analysis is shown for each factor included in the single regression.

Predictor variables	n	Single regression			p-to-exit	Multiple regression		
		p-value	OR	95%CI		p-value	OR	95%CI
Gender								
Men	46	-	-	-	-	-	-	-
Women	265	0.000	10.0	4.92–20.51	–	0.000	6.4	2.38–16.99
Cervicalgia								
No	92	-	-	-	-	-	-	-
Yes	217	0.000	35.6	13.41–94.62	-	0.000	10.3	3.37–31.44
Body pain								
No	164	-	--	-	-	-	-	-
Yes	146	0.000	12.6	4.40–36.15	-	0.041	3.8	1.06–13.53
MED								
No	167	-	-	-	-	-	-	-
Yes	144	0.034	2.0	1.06–3.94	0.156	-	-	--
ENT								
No	154	-	-	-	-	-	-	-
Yes	157	0.016	2.0	1.16–4.25	0.064	-	-	-
Diabetes								
No	299	-	-	-	-	-	-	-
Yes	12	0.337	2.0	0.50–7.42	-	-	-	-
Cardiorespiratory conditions								
No	233	-	-	-	-	-	-	-
Yes	78	0.171	1.8	0.78–3.94	-	-	-	-
Gastritis/Ulcer								
No	222	-	-	-	-	-	-	-
Yes	89	0.012	3.1	1.28–7.67	0.274	-	-	-
NSPS								
No	60	-	-	-	-	-	-	-
Yes	251	0.000	24.0	11.24–51.02	-	0.000	7.1	2.81–18.06

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indicated that gender [OR = 2.8 (CI = 1.13–6.86)], diabetes [OR = 4.5 (CI = 1.23–15.55)] and NSPS [OR = 6.8 (CI = 3.16–14.64)] were significantly associated with the presence of painful TMD and M. There were no signs of multicollinearity among the predictor variables.

Discussion

TMD has been included in a group of painful conditions named functional pain syndromes, or idiopathic pain disorders.[1] These conditions are associated with neurobiological, physiological and

Table 4. Single and multiple logistic regression models for prediction of TMD+M group versus TMD only group. The number of cases (n) included in the analysis is shown for each factor included in the single regression.

Predictor variables	n	Single regression			p-to-exit	Multiple regression		
		p value	OR	95%CI		p-value	OR	95%CI
Gender								
Men	34	-	-	-	-	-	-	-
Women	271	0.001	3.8	1.7–8.65	-	0.026	2.8	1.13–6.86
Cervicalgia								
No	67	-	-	-	-	-	-	-
Yes	235	0.001	3.1	1.55–6.30	0.232	-	-	-
Body pain								
No	144	-	-	-	-	-	-	-
Yes	159	0.178	1.6	0.81–3.11	-	-	-	-
MED								
No	158	-	-	-	-	-	-	-
Yes	147	0.555	1.2	0.63–2.36	-	-	-	-
ENT								
No	143	-	-	-	-	-	-	-
Yes	162	0.794	1.1	0.56–2.10	-	-	-	-
Diabetes								
No	291	-	-	-	-	-	-	-
Yes	14	0.019	3.9	1.24–12.39		0.019	4.5	1.23–15.55
Cardiorespiratory conditions								
No	225	-	-	-	-	-	-	-
Yes	80	0.774	1.1	0.52–2.40	-	-	-	-
Gastritis/Ulcer								
No	209	-	-	-	-	-	-	-
Yes	96	0.973	1.01	0.49–2.05	-	-	-	-
NSPS								
No	45	-	-	-	-	-	-	-
Yes	260	< 0.001	7.9	3.79–16.49	-	< 0.001	6.8	3.16–14.64

anatomical changes in the central nervous system.[24] It is also well established that there is a comorbid relationship between painful TMD and M.[10,13] Previous studies have demonstrated that TMD patients, as well as migraineurs, are more sensitive to pain and present multiple BP areas more frequently.[4,19,25] These characteristics point to a generalized dysfunction of the nociceptive system, and an upregulation of the nociceptive process.[26] Herein, we hypothesized that the presence of a comorbidity (painful TMD associated with M) could be associated with a higher prevalence of other painful conditions and systemic diseases.

Our most important findings were: a) individuals with painful TMD and M presented higher prevalence

Table 5. Single and multiple logistic regression models for prediction of TMD+M group versus TMD only group. The number of cases (n) included in the analysis is shown for each factor included in the single regression.

Predictor variables	n	Single regression			p-to-exit	Multiple regression		
		p-value	OR	95%CI		p-value	OR	95%CI
Gender								
Men	34	-	-	-	-	-	-	-
Women	271	0.001	3.8	1.7–8.65	–	0.026	2.8	1.13–6.86
Cervicalgia								
No	67	-	-	-	-	-	-	-
Yes	235	0.001	3.1	1.55–6.30	0.232	-	-	-
BP								
No	144	-	-	-	-	-	-	-
Yes	159	0.178	1.6	0.81–3.11	-	-	-	-
MED								
No	158	-	-	-	-	-	-	-
Yes	147	0.555	1.2	0.63–2.36	-	-	-	-
ENT								
No	143	-	-	-	-	-	-	-
Yes	162	0.794	1.1	0.56–2.10	-	-	-	-
Diabetes								
No	291	-	-	-	-	-	-	-
Yes	14	0.019	3.9	1.24–12.39	–	0.019	4.5	1.23–15.55
Cardiorespiratory conditions								
No	225	-	-	-	-	-	-	-
Yes	80	0.774	1.1	0.52–2.40	-	-	-	-
Gastritis/Ulcer								
No	209	-	--	-	-	-	-	-
Yes	96	0.973	1.01	0.49–2.05	-	-	-	-
NSPS								
No	45	-	-	-	-	-	-	-
Yes	260	< 0.001	7.9	3.79–16.49	–	< 0.001	6.8	3.16–14.64

TMD: Temporomandibular disorders; M: Migraine; MED: Musculoskeletal disorders; ENT: Ear, nose and throat disorders; NSPS: Non-specific physical symptoms.

of all the painful conditions and systemic diseases investigated; b) cervicalgia was significantly associated with the presence of painful TMD, compared with the condition of the controls; c) gender, cervicalgia, BP and NSPS were significantly associated with the presence of a comorbidity (painful TMD+M), compared with the condition of the controls; d) when comparing individuals with TMD, the presence of M (comorbid group) was associated with gender, diabetes and NSPS.

In our results, the report of persistent cervicalgia figured as an important factor associated with TMD only or TMD+M. Previous studies have shown that cervicalgia

is both associated with and a predictor of TMD,[8,27] as is M.[28] Among the hypotheses about the mechanisms related to these associations, the anatomical aspects seem to be particularly relevant. Muscles and ligaments of the cranial area are connected in the cervical region, possibly resulting in an interaction among such factors as neck muscle activity, head position, and mandibular function.[29] Moreover, there is a convergence of cervical and trigeminal inputs with the spinal trigeminal nucleus, resulting in referred pain.[2]

In the present study, both TMD and M were more prevalent among adult women than men. In the univariate regression, gender was significantly associated with both groups (TMD only and TMD+M), whereas in the multiple regressions, it figured as a significant predictor only for the comorbid group. Similar results were found by other authors with a higher prevalence in women[10,30] aged 20 to 40 years.[30] These differences may be attributed to the different activation of the endogenous analgesia system and the central processing of nociceptive stimuli between genders. Moreover, sexual hormones, especially estrogen, have been pointed out as playing an important role in sensitivity to pain, altering the pain threshold and tolerance according to the menstrual cycle phase. TMD onset tends to occur after puberty, and the increase in the severity of signs and symptoms generally reaches its peak during the reproductive age, with higher prevalence in young adult women.[30]

In our sample, the presence of diffuse BP was significantly associated with comorbidity. It has been reported that multiple pain conditions elsewhere in the body could predict TMD onset,[31] and influence its maintenance.[32] Migraineurs are also more likely to report BP.[25] It is plausible to hypothesize that this association could be related to central sensitization and functional changes in genetically susceptible individuals.[33] Previous evidence supports the theory that the activation and sensitization of the trigeminovascular system may result in the impairment of diffuse noxious inhibitory control,[34] predisposing to a progressive development of cephalic and whole-body cutaneous allodynia.[35] This evidence is consistent with our findings, considering that the association between M and TMD may reflect a more severe state of sensitization.

Although more studies are needed to improve the understanding of the mechanisms involved in comorbid conditions, our results are aligned with the evidence pointing to the relevant role of the central and peripheral nervous systems. Structural and functional aspects have to be considered, in addition to the influence of other aspects, such as genetics and psychosocial alterations.[1,28,37]

We can conclude that individuals with a comorbidity (M associated with painful TMD) show a more severe condition, as evidenced by the higher number of predictor variables, compared with individuals with only painful TMD. This finding strongly entails impairment of the endogenous mechanisms of pain control, which should be considered in all processes, from diagnosis to treatment plan.

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