Salivary Levels of Interleukin-1β in Temporomandibular Disorders and Fibromyalgia

Patrícia S. Cê, DDS*
PhD Student

Bernardo B. O. Barreiro, DDS*
MSc Student

Programa de Pós-graduação em Odontologia
Escola de Ciências da Saúde
Porto Alegre, Brazil

Rodrigo B. M. Silva, Pharmacist
PhD Student
Programa de Pós-graduação em Medicine e Ciências da Saúde
Escola de Medicina
Centro de Pesquisas em Toxicologia e Farmacologia
Escola de Ciências da Saúde
Porto Alegre, Brazil

Rogério B. Oliveira, DDS, PhD
Professor

Claiton Heitz, DDS, PhD
Professor

Programa de Pós-graduação em Odontologia
Escola de Ciências da Saúde
Porto Alegre, Brazil

Maria M. Campos, DDS, PhD
Professor
Programa de Pós-graduação em Odontologia
Escola de Medicina
Centro de Pesquisas em Toxicologia e Farmacologia
Escola de Ciências da Saúde
Porto Alegre, Brazil

**Both authors contributed equally to the experiments.*

Correspondence to:
Dr Maria M. Campos
School of Dentistry and Institute of Toxicology and Pharmacology
Pontifical Catholic University of Rio Grande do Sul
Avenida Ipiranga 6681, Partenon, 90619-900, Porto Alegre, RS, Brazil
Email: maria.campos@pucrs.br; camposmmartha@yahoo.com

Aims: To evaluate salivary levels of the proinflammatory cytokine interleukin-1β (IL-1β) in patients with temporomandibular disorders (TMD), fibromyalgia, or both conditions in comparison to healthy individuals. **Methods:** A total of 69 females (18 to 84 years of age) were assigned to one of four groups: (A) healthy controls (n = 27); (B) TMD only (n = 18); (C) fibromyalgia only (n = 15); and (D) fibromyalgia plus TMD (n = 9). Clinical data and salivary IL-1β levels were evaluated. Statistical analysis was performed by using Fischer exact test, unpaired Student *t* test, or one-way analysis of variance plus multiple comparisons Tukey test, depending on the variable. The correlation between age and IL-1β levels was assessed by using Pearson correlation coefficient. **Results:** Most patients in groups B and D displayed clinical features of Group I (muscle disorders) and Group II (disc displacements) of the Axis I Research Diagnostic Criteria for Temporomandibular Disorders. The subjects in groups C and D presented values of > 7 on the Widespread Pain Index (WPI) and > 5 for Symptom Severity Score (SS) according to the Fibromyalgia Survey Diagnostic Criteria and Severity Scale. There were no significant differences when SS and WPI levels were compared between groups C and D. The patients with TMD showed significantly higher salivary IL-1β levels irrespective of a fibromyalgia diagnosis (groups B and D), whereas the fibromyalgia-only patients (group C) did not show any significant difference in relation to controls. **Conclusion:** This study provides novel evidence indicating that salivary IL-1β may be a biomarker for TMD. *J Oral Facial Pain Headache 2018;32:130–136. doi: 10.11607/ofph.1899*

Keywords: *fibromyalgia, IL-1β, patients, saliva, temporomandibular disorders*

Fibromyalgia is a chronic widespread pain syndrome that is commonly accompanied by morning fatigue, anxiety, headache, mood disorders, and stress that reduces the quality of life (QoL) of the affected individuals.[1,2] Patients diagnosed with temporomandibular disorders (TMD) also report some of these symptoms, including chronic fatigue, sleep dysfunction, and long-lasting pain.[3–5] The term TMD defines a series of alterations affecting the temporomandibular joint (TMJ) and associated muscular and skeletal tissues.[6,7] There is compelling evidence indicating a comorbidity between TMD and fibromyalgia, and many patients diagnosed with fibromyalgia exhibit signs and symptoms of TMD.[8] Moreover, a higher prevalence of migraine and chronic fatigue syndrome has been observed in patients presenting myofascial TMD pain, as indicated by an analysis of self-reported comorbidities.[9] It is noteworthy that it has been proposed that TMD might represent a functional central pain syndrome, such as fibromyalgia or chronic fatigue syndrome.[10]

Evidence has accumulated that links the pathophysiology of TMD and fibromyalgia to an unbalanced production of pro- and anti-inflammatory cytokines. For instance, patients with TMD displayed higher levels of several proinflammatory cytokines in the synovial fluid, such as interleukin-1β (IL-1β), tumor necrosis factor, interleukin-6 (IL-6), and interleukin-8 (IL-8), and these levels were correlated with degenerative alterations and treatment failures.[11–13] More recently, it has been proposed that higher plasma levels of the same proinflammatory cytokines, in addition to the anti-inflammatory cytokine interleukin-10 (IL-10), are related to sleep disturbances in

Table 1 Demographic and Clinical Features of the Women Enrolled in the Study

Groups	Control	TMD	Fibromyalgia	Fibromyalgia + TMD
n	27	18	15	9
Age range (y)	20–77	18–67	49–84	26–59
Median age (y)	40	49.5	55	53
Mean ± SEM age (y)	40 ± 3	46 ± 4	59 ± 2**	51 ± 4
Lower 95% CI of mean	33.2	37.6	53.4	43.4
Upper 95% CI of mean	46.8	53.9	63.8	58.9
Mouth opening > 35 mm (n)	27	15	11	9
RDC Axis 1 classification (n)				
Group I	–	3	–	1
Group II	–	6	–	–
Groups I/II	–	9	–	7

TMD = temporomandibular disorder; CI = confidence interval; SEM = standard error of the mean. **$P < .01$ in comparison to the control group (one-way analysis of variance followed by Tukey multiple comparisons test).

TMD-diagnosed individuals.[14] A recent systematic review has described controversial data about the variations in cytokine levels in the synovial fluid of patients with TMD.[15] For patients with fibromyalgia, there is a series of publications showing increased or decreased levels of cytokines according to the evaluation of plasma or serum samples, whereas some studies did not detect significant changes in the production of systemic cytokines.[16–19] It is not clear whether the dysregulation in cytokine production is linked to the comorbidities observed in fibromyalgia patients such as anxiety, fatigue, depression, and sleep alterations.[20–23] It is also noteworthy that levels of IL-8 were found to be increased in the cerebrospinal fluid of individuals with fibromyalgia,[24] suggesting a role of central inflammation in this syndrome. In contrast, no significantly altered cytokine levels were detected in skin biopsies or in muscle microdialysis samples of patients with fibromyalgia when compared to healthy controls.[25,26] Therefore, the aim of the present study was to evaluate salivary levels of the pro-inflammatory cytokine IL-1β in patients with TMD, fibromyalgia, or both conditions in comparison to healthy controls. Attempts were also made to correlate the salivary levels of IL-1β with the clinical findings in the different groups of patients.

Materials and Methods

Ethical Concerns

The Institutional Ethics Committee reviewed and approved all the experimental protocols (report number 844208). Informed consent was obtained from all participants included in the study. The subjects were appropriately informed about the procedures and the guarantee of anonymity.

Participants

The study enrolled 69 females aged between 18 and 84 years and distributed them into four groups: (A) healthy controls (n = 27); (B) patients diagnosed with TMD (n = 18); (C) patients diagnosed with fibromyalgia (n = 15); and (D) patients diagnosed with fibromyalgia plus TMD (n = 9). The patients were recruited from the Department of Prosthodontics, School of Dentistry, and from the Rheumatology Service, Hospital São Lucas (both from Pontifícia Universidade Católica do Rio Grande do Sul [PUCRS], Brazil). Healthy controls who did not present diagnostic criteria for either TMD or fibromyalgia were selected from the academic community. Individuals using complete prostheses or orthodontic devices, those who had previously received any invasive procedure involving the TMJ, those diagnosed with autoimmune or periodontal dise ases, and those with a previous history of alcoholism and/or tobacco use were excluded from the study. A preceding history of chemotherapy or radiotherapy was also considered as an exclusion criterion. Demographic and clinical features of the study sample are provided in Table 1.

Clinical Procedures

Medical history, including the regular use of any medicine, was taken for all participants. A complete intraoral clinical examination was also performed. An experienced clinician carried out the TMD diagnosis by using the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD).[27] Axis I of the RDC/TMD instrument was applied for all the experimental groups for the assessment of TMD-related physical alterations.

A practicing rheumatologist performed the diagnosis of the fibromyalgia patients. The patients in groups C and D were evaluated by the Fibromyalgia Survey Diagnostic Criteria and Severity Scale (FSDC) for determining the Widespread Pain Index (WPI) and the Symptom Severity Score (SS), as described previously.[28] The criteria for a fibromyalgia diagnosis included a WPI > 7 and an SS > 5. Alternatively, the criteria were met when the WPI ranged from 3 to 6 and the SS was > 9. In both cases, the symptoms had to be regular (ie, presenting similar levels for up to 3 months[29]).

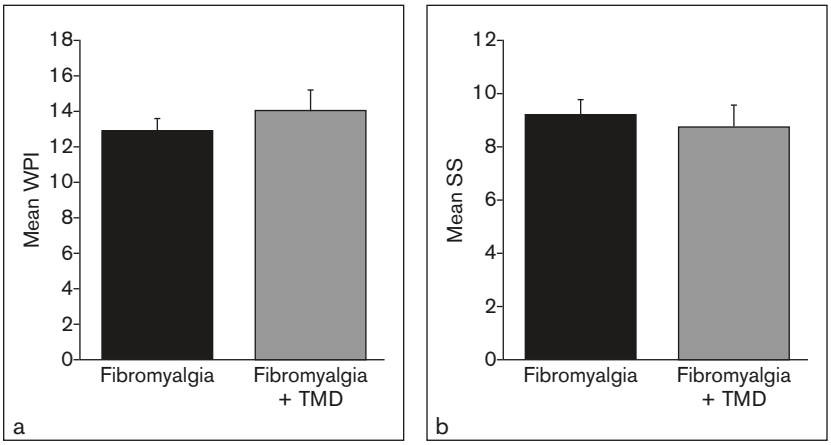

Fig 1 Comparison of **(a)** Widespread Pain Index (WPI) and **(b)** Symptom Severity Score (SS) in patients diagnosed with fibromyalgia (n = 15) or fibromyalgia + temporomandibular disorder (TMD) (n = 9). Unpaired Student *t* test revealed no significant differences between the groups ($P > .05$ for both analyzed parameters).

Determination of Salivary IL-1β Levels

For saliva collection, the methodology described previously was employed.[30] The patients were required not to eat for at least 1 hour before the collection. Following a mouthwash with water, the patients were instructed to rest in the seated position for 5 minutes. Saliva was collected in 5-mL graduated vials and immediately stored at −20°C until analysis.

Salivary levels of IL-1β were determined by using sandwich enzyme-linked immunosorbent assay (ELISA) using a commercial kit (DY201; Human IL-1β/IL-1F2 DuoSet ELISA) according to the manufacturer's instructions (R&D Systems). The samples were rapidly centrifuged before plating. The results are expressed in picograms per milliliter.

Statistical Analyses

Data are presented as the percentage and absolute number of patients in each group for use of different classes of drugs and as the mean ± standard error of the mean (SEM) for age, WPI and SS scores, and IL-1β levels. The frequency data were compared by using Fischer exact test. For WPI and SS scores, unpaired Student *t* test was used. The comparison of mean ages and salivary IL-1β levels was performed by using one-way analysis of variance (ANOVA) followed by the multiple comparisons Tukey test. To analyze the possible correlation between age and salivary IL-1β levels, the Pearson correlation coefficient was employed. *P* values less than .05 were considered to be indicative of statistical significance. GraphPad Software Prism 5.1 was used for all analyses (GraphPad Software).

Results

The demographic characteristics of the included participants are presented in Table 1. Only women were included in this study, and the age of the recruited individuals ranged from 18 to 84 years. The statistical comparison of the mean age in each group (one-way ANOVA, followed by Tukey post hoc test) revealed a significant difference for the patients allocated into group C in relation to group A ($P < .01$). There was no significant difference in comparison to the other groups (B and D) ($P > .05$).

The clinical evaluation showed that all the patients in groups A and D presented a mouth-opening value greater than 35 mm. In contrast, 3 out of 18 and 4 out of 15 patients in groups B and C, respectively, presented mouth-opening values less than 35 mm. Most patients in groups B and D displayed clinical features of Group I (muscle disorders) and Group II (disc displacements) on Axis I of the RDC/TMD instrument (Table 1).

All patients in groups C and D fulfilled the preliminary diagnostic criteria for fibromyalgia, presenting with WPI > 7 and SS > 5. Of note, there were no significant differences when SS and WPI levels were compared between these two groups ($P > .05$; unpaired Student *t* test) (Fig 1).

Anamnesis revealed that the most common drugs used by the patients included analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs; including ibuprofen, diclofenac, nimesulide, and naproxen associated or not with omeprazole), antidepressants (including amitriptyline, duloxetine, fluoxetine, and sertraline), anti-hypertensive drugs, and oral contraceptives. The frequency of use of the different classes of drugs and the absolute number of patients in each group are depicted in Fig 2. Fischer exact test revealed a significant difference for use of analgesics in group C ($P < .01$). Analgesic drugs included the classical non-opioid (acetaminophen or dipyrone) or opioid drugs (tramadol). In some cases, the patients used pharmaceutical formulations containing acetaminophen plus the muscle relaxant agent cyclobenzaprine. Furthermore, the anticonvulsant pregabalin and the anti-rheumatic drug hydroxychloroquine were also considered in the category of analgesics, as they were used for pain relief by some patients with fibromyalgia.

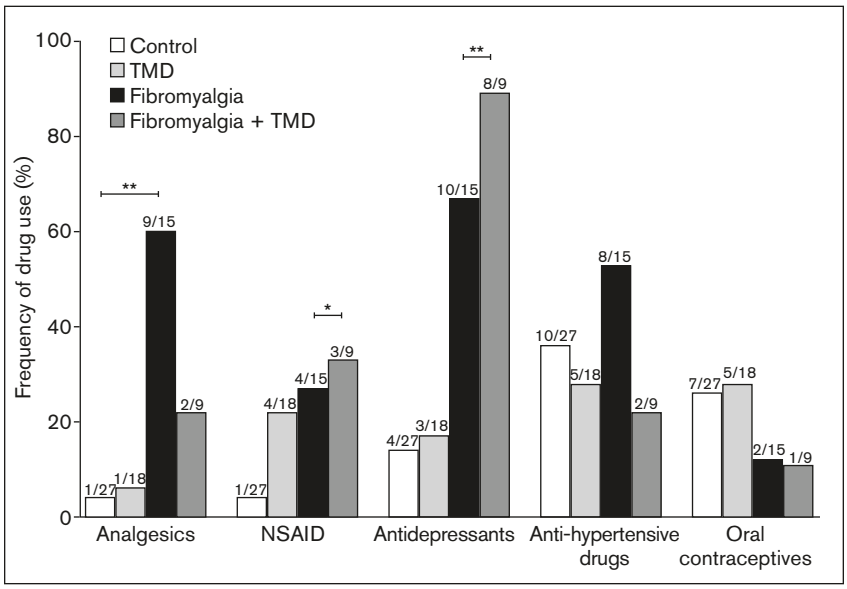

Fig 2 Percentage of individuals using different classes of drugs in the experimental groups. The absolute number of patients using the drug in each group is indicated at the top of each column. Only the most cited drugs were considered for this analysis. Fischer exact test was used to compare the frequency of the use of each drug class between the different experimental groups in relation to the control group (n = 27) (*P < .05; **P < .01).

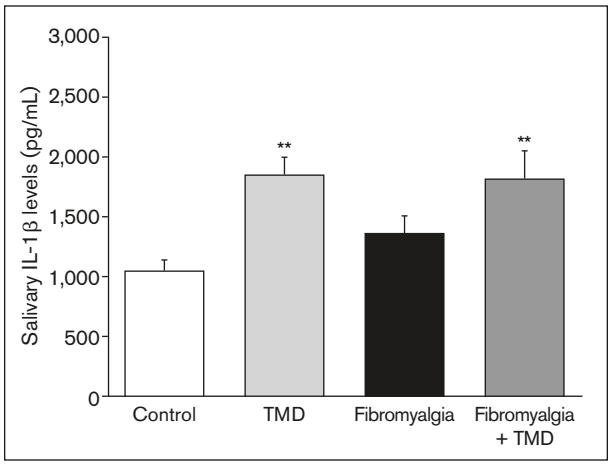

Fig 3 Mean ± standard error of the mean (SEM) salivary levels of interleukin-1β (IL-1β) in the different experimental groups (control = 27; TMD = 18; fibromyalgia = 15; fibromyalgia + TMD = 9). **P < .01 in comparison to control individuals (one-way analysis of variance followed by Tukey multiple comparison test).

There was a significant difference in the proportion of individuals reporting use of NSAIDs in groups C and D when compared with group A (P < .05); however, the number of subjects using NSAIDs in group B in comparison to the number in group A was not significantly different (P = .141). The use of antidepressants was also significantly different between groups C and D (P < .01; Fischer exact test). No significant differences were observed for the use of anti-hypertensive drugs or oral contraceptives (P > .05) when group B, C, or D was compared with group A.

Data in Fig 3 demonstrate that patients with TMD displayed higher salivary IL-1β levels regardless of their fibromyalgia diagnosis (groups B and D). The statistical comparison (one-way ANOVA followed by Tukey post hoc test) revealed significant differences (P < .01) when groups B and D were compared with group A. There was no significant difference between group C and group A (P > .05).

Pearson correlation coefficients were used to analyze whether the age variations in the different experimental groups affected the salivary IL-1β levels. There was no significant correlation between age and IL-1β levels (P > .05) in groups A (ρ = −0.042), B (ρ = −0.02150), C (ρ = 0.171), or D (ρ = 0.186). An overall analysis of age vs the salivary IL-1β levels including all 69 patients enrolled in the study did not reveal any negative or positive correlation between these parameters (P > .05; ρ = 0.068).

Discussion

The pathophysiology of fibromyalgia and TMD has been associated with variations of cytokine levels, although further studies on this matter are still required. Data from the available literature are quite controversial, showing increased, diminished, or unchanged

levels of cytokines in patients with fibromyalgia or TMD according to the evaluation of distinct biologic matrices, such as plasma and synovial fluid. The present study is the first to analyze the salivary levels of IL-1β in patients diagnosed with TMD, fibromyalgia, or both conditions.

The limitations of the present study—including the age variation, small female sample, assessment of a unique cytokine, and the method used for saliva collection—must be considered for adequate interpretation of data. Firstly, the mean age of the group with fibromyalgia (C) was significantly higher in relation to the control (A). The mean age of patients with fibromyalgia plus TMD (D) was also superior, although significant differences were not observed in relation to the control (A). In agreement with the present data, both fibromyalgia and TMD display age- and sex-related differences, predominantly in middle-aged women.[31–34] Second, the sample was comprised of only women, and limiting the study population to females might also be considered as an additional drawback in the present study. However, it is important to mention that only women attended the Rheumatology Service of Hospital São Lucas (PUCRS, Brazil) for fibromyalgia diagnosis and treatment during the period of sample collection. Previous studies conducted in other countries including patients with TMD and comorbidities (such as sleep disturbance and fibromyalgia) also had samples composed exclusively of women.[14,35]

There were no significant differences when comparing mouth-opening values among the groups, and most patients with TMD or TMD plus fibromyalgia presented myofascial pain and disc displacement, as revealed by Axis I of the RDC/TMD instrument. The FSDC showed similar SS and WPI levels in patients with fibromyalgia despite the presence of TMD. These results confirm previous data suggesting that myofascial pain without accompanying mouth-opening limitations was the most prevalent alteration observed in subjects with fibromyalgia plus TMD.[36] Furthermore, the prevalence of fibromyalgia in patients with TMD is around 20%, and individuals with both conditions might display various common symptoms indicative of altered central pain mechanisms.[33,35,37]

In this study, some patients with TMD and/or fibromyalgia reported the utilization of NSAIDs (such as ibuprofen, diclofenac, nimesulide, and naproxen associated or not with omeprazole) for gastrointestinal protection. Of note, there was a higher use of analgesics in the fibromyalgia group and for the use of antidepressants in either group diagnosed with fibromyalgia regardless of TMD comorbidity. The patients in the fibromyalgia group reported use of acetaminophen, dipyrone, and opioids (mainly tramadol), associated or not with muscle relaxants (mostly cyclobenzaprine). Some patients were also under treatment with the anticonvulsant agent pregabalin or the anti-rheumatic drug hydroxychloroquine for pain control. The most used antidepressants in the fibromyalgia groups included amitriptyline, duloxetine, fluoxetine, and sertraline. The treatment of chronic pain disorders involves both nonpharmacologic and pharmacologic approaches. Recently, the guidelines for fibromyalgia management have been revised,[38] indicating nonpharmacologic methods as first-line therapy, with individualized pharmacotherapy depending on the patient outcomes. According to this publication, the main drugs used for pain management are duloxetine, pregabalin, and tramadol (combined or not with acetaminophen), whereas recommendations for fibromyalgia-related sleep disorders include low doses of amitriptyline, cyclobenzaprine, and pregabalin at night,[38] which is consistent with the present findings.

Cytokines are small regulatory proteins secreted by immune cells in both the peripheral and the central nervous systems. It has been suggested that persistent elevation of cytokines causes tissue injury and altered nociceptor function.[39,40] The ELISA assay in the present study revealed that TMD was associated with higher salivary levels of IL-1β regardless of a fibromyalgia diagnosis in comparison to healthy control subjects. In fact, elevated cytokine levels have been correlated with greater pain sensitivity, perceived stress, and depressed mood, which are phenotypic characteristics of chronic pain conditions such as TMD.[41,42] Furthermore, a recent systematic review described that five of seven selected studies showed an increase in the synovial levels of IL-1β in patients with TMD, linking the augmentation of this cytokine to TMD-related cartilage degradation and clinical symptoms.[15] Therefore, it is possible that specific alterations inherent to TMD, such as fibrocartilage and subchondral bone damage, may show a positive correlation with salivary IL-1β levels, a parameter unaffected by the concomitant diagnosis of fibromyalgia. In the present study, IL-1β was detected even in healthy control patients. Corroborating these findings, detectable IL-1β contents were found in the saliva of healthy control subjects with a mean age similar to that of the present study.[43,44]

Considering the use of different classes of drugs by the patients enrolled in the present study, the higher consumption of analgesic drugs by the fibromyalgia group might have a modulatory effect on the salivary IL-1β levels in this set of patients despite their primary mechanisms of action not involving interference with cytokines. Conversely, the use of antidepressants does not appear to have any influence on IL-1β levels, as both groups with a TMD diagnosis presented higher salivary levels of this cytokine despite the greater number of patients taking antidepressants in groups with fibromyalgia. The same

observation can be made for the use of NSAIDs, as the percentage of usage was similar when comparing groups B, C, and D with healthy controls (group A). The absence of significant differences for the intake of antihypertensive drugs or oral contraceptives suggests that these drugs may not have influenced the salivary IL-1β levels in the present study. Nonetheless, it is not possible to discount an interference by antihypertensive drugs on the levels of this cytokine in patients with fibromyalgia without TMD due to the high number of patients taking this drug class in group C (> 50% of individuals).

Additional studies investigating the salivary cytokine levels in a larger sample of TMD and fibromyalgia patients are still required. This is especially relevant when considering that saliva collection does not require any invasive procedure and might represent an adjuvant tool for determining biomarkers of chronic pain and other neurologic alterations.[45] The salivary levels of cortisol were proportional to the scores of depression and somatization in young individuals of both sexes with a TMD diagnosis,[46] and furthermore, a positive correlation between pain catastrophizing and salivary cortisol levels has been reported in a sample of healthy individuals and TMD patients predominantly formed by young women.[47] On the other hand, morning salivary levels of cortisol were shown to be slightly elevated in patients with shoulder and neck pain, whereas fibromyalgia patients presented lower salivary cortisol levels when compared to healthy control subjects.[48] In addition, a subtle increase in salivary cortisol has been reported to be associated with major depression in patients diagnosed with fibromyalgia.[49]

The present study has provided preliminary evidence linking increased salivary IL-1β levels to TMD but not to fibromyalgia. Thus, this possibility needs further research, and the limitations of the present study—including the broad use of central analgesic drugs by the fibromyalgia patients—must be taken into account. In addition, the salivary levels of this cytokine require additional investigation in younger subjects with fibromyalgia with or without TMD, and the salivary production of distinct pro- and anti-inflammatory cytokines deserves further analysis. In the present study, there was a great variation in age among the groups that might have influenced the salivary IL-1β levels. Therefore, Pearson correlation coefficient was employed to analyze the possible negative or positive correlation between age and IL-1β levels. The results did not reveal any significant correlation, even when performing an overall analysis including all 69 patients enrolled in the study. Therefore, a TMD diagnosis, rather than age variation, appeared to modulate the salivary production of IL-1β in the present study.

Conclusions

Altogether, these data indicate that increased salivary levels of the pro-inflammatory cytokine IL-1β might represent a useful biomarker for TMD.

Acknowledgments

P.S.C, B.B.O.B., and R.B.M.S. receive scholarships from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES, Brazil). M.M.C. is a research career awardee of the National Council for Scientific and Technological Development of Brazil (CNPq/303842-2014-8). The authors would like to thank Dr Regênio M. Herbstrith Segundo (Department of Prosthodontics, School of Dentistry, PUCRS, Brazil) and Dr Marco Aurélio Goldenfum (Rheumatology Service, Hospital São Lucas, PUCRS, Brazil) for their valuable help in selecting patients. The authors report no conflicts of interest.

References

1. Mease P, Arnold LM, Bennett R, et al. Fibromyalgia syndrome. J Rheumatol 2007;34:1415–1425.
2. Walters A, Tolle SL, McCombs GM. Fibromyalgia syndrome: Considerations for dental hygienists. J Dent Hyg 2015;89:76–85.
3. Sommer I, Lavigne G, Ettlin DA. Review of self-reported instruments that measure sleep dysfunction in patients suffering from temporomandibular disorders and/or orofacial pain. Sleep Med 2015;16:27–38.
4. Ahmad M, Schiffman EL. Temporomandibular joint disorders and orofacial pain. Dent Clin North Am 2016;60:105–124.
5. Robinson LJ, Durham J, Newton JL. A systematic review of the comorbidity between temporomandibular disorders and chronic fatigue syndrome. J Oral Rehabil 2016;43:306–316.
6. Shaffer SM, Brismée JM, Sizer PS, Courtney CA. Temporomandibular disorders. Part 1: Anatomy and examination/diagnosis. J Man Manip Ther 2014;22:2–12.
7. Yule PL, Durham J, Wassell RW. Pain part 6: Temporomandibular disorders. Dent Update 2016;43:39–48.
8. Dahan H, Shir Y, Velly A, Allison P. Specific and number of comorbidities are associated with increased levels of temporomandibular pain intensity and duration. J Headache Pain 2015;16:528.
9. Dahan H, Shir Y, Nicolau B, Keith D, Allison P. Self-reported migraine and chronic fatigue syndrome are more prevalent in people with myofascial vs nonmyofascial temporomandibular disorders. J Oral Facial Pain Headache 2016;30:7–13.
10. Furquim BD, Flamengui LM, Conti PC. TMD and chronic pain: A current view. Dental Press J Orthod 2015;20:127–133.
11. Kaneyama K, Segami N, Nishimura M, Suzuki T, Sato J. Importance of proinflammatory cytokines in synovial fluid from 121 joints with temporomandibular disorders. Br J Oral Maxillofac Surg 2002;40:418–423.
12. Nishimura M, Segami N, Kaneyama K, Sato J, Fujimura K. Comparison of cytokine level in synovial fluid between successful and unsuccessful cases in arthrocentesis of the temporomandibular joint. J Oral Maxillofac Surg 2004;62:284–287.

13. Gulen H, Ataoglu H, Haliloglu S, Isik K. Proinflammatory cytokines in temporomandibular joint synovial fluid before and after arthrocentesis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2009;107:e1–e4.
14. Park JW, Chung JW. Inflammatory cytokines and sleep disturbance in patients with temporomandibular disorders. J Oral Facial Pain Headache 2016;30:27–33.
15. Kellesarian SV, Al-Kheraif AA, Vohra F, et al. Cytokine profile in the synovial fluid of patients with temporomandibular joint disorders: A systematic review. Cytokine 2016;77:98–106.
16. Uçeyler N, Häuser W, Sommer C. Systematic review with meta-analysis: Cytokines in fibromyalgia syndrome. BMC Musculoskelet Disord 2011;12:245.
17. Rodriguez-Pintó I, Agmon-Levin N, Howard A, Shoenfeld Y. Fibromyalgia and cytokines. Immunol Lett 2014;161:200–203.
18. Sturgill J, McGee E, Menzies V. Unique cytokine signature in the plasma of patients with fibromyalgia. J Immunol Res 2014; 2014:938576.
19. Tsilioni I, Russell IJ, Stewart JM, Gleason RM, Theoharides TC. Neuropeptides CRH, SP, HK-1, and inflammatory cytokines IL-6 and TNF are increased in serum of patients with fibromyalgia syndrome, implicating mast cells. J Pharmacol Exp Ther 2016;356:664–672.
20. Gür A, Karakoç M, Nas K, et al. Cytokines and depression in cases with fibromyalgia. J Rheumatol 2002;29:358–361.
21. García-Lozano JR, Capilla-Sevilla C, García-López O, Moreno-Gallego I. Correlation between cytokines and anxious-depressive symptoms in patients with fibromyalgia. Reumatol Clin 2008;4:136–139.
22. Nakamura T, Schwander SK, Donnelly R, et al. Cytokines across the night in chronic fatigue syndrome with and without fibromyalgia. Clin Vaccine Immunol 2010;17:582–587.
23. Dell'Osso L, Bazzichi L, Baroni S, et al. The inflammatory hypothesis of mood spectrum broadened to fibromyalgia and chronic fatigue syndrome. Clin Exp Rheumatol 2015;33(suppl):s109–s116.
24. Kadetoff D, Lampa J, Westman M, Andersson M, Kosek E. Evidence of central inflammation in fibromyalgia-increased cerebrospinal fluid interleukin-8 levels. J Neuroimmunol 2012;242:33–38.
25. Üçeyler N, Kewenig S, Kafke W, Kittel-Schneider S, Sommer C. Skin cytokine expression in patients with fibromyalgia syndrome is not different from controls. BMC Neurol 2014;14:185.
26. Christidis N, Ghafouri B, Larsson A, et al. Comparison of the levels of pro-inflammatory cytokines released in the vastus lateralis muscle of patients with fibromyalgia and healthy controls during contractions of the quadriceps muscle—A microdialysis study. PLoS One 2015;10:e0143856.
27. Schiffman E, Ohrbach R. Executive summary of the Diagnostic Criteria for Temporomandibular Disorders for clinical and research applications. J Am Dent Assoc 2016;147:438–445.
28. Wolfe F, Clauw DJ, Fitzcharles MA, et al. Fibromyalgia criteria and severity scales for clinical and epidemiological studies: A modification of the ACR Preliminary Diagnostic Criteria for Fibromyalgia. J Rheumatol 2011;38:1113–1122.
29. Wolfe F, Clauw DJ, Fitzcharles MA, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res (Hoboken) 2010;62:600–610.
30. Hoffmann RR, Yurgel LS, Campos MM. Evaluation of salivary endothelin-1 levels in oral squamous cell carcinoma and oral leukoplakia. Regul Pept 2011;166:55–58.
31. Yunus MB. The role of gender in fibromyalgia syndrome. Curr Rheumatol Rep 2001;3:128–134.
32. Yunus MB. Gender differences in fibromyalgia and other related syndromes. J Gend Specif Med 2002;5:42–47.
33. Hoffmann RG, Kotchen JM, Kotchen TA, Cowley T, Dasgupta M, Cowley AW Jr. Temporomandibular disorders and associated clinical comorbidities. Clin J Pain 2011;27:268–274.
34. Arnold LM, Choy E, Clauw DJ, et al. Fibromyalgia and chronic pain syndromes: A white paper detailing current challenges in the field. Clin J Pain 2016;32:737–746.
35. Janal MN, Raphael KG, Cook DB, Sirois DA, Nemelivsky L, Staud R. Thermal temporal summation and decay of after-sensations in temporomandibular myofascial pain patients with and without comorbid fibromyalgia. J Pain Res 2016;9:641–652.
36. Fraga BP, Santos EB, Farias Neto JP, et al. Signs and symptoms of temporomandibular dysfunction in fibromyalgic patients. J Craniofac Surg 2012;23:615–618.
37. Yunus MB. The prevalence of fibromyalgia in other chronic pain conditions. Pain Res Treat 2012;2012:584573.
38. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. Ann Rheum Dis 2017;76:318–328.
39. Verri WA Jr, Cunha TM, Parada CA, Poole S, Cunha FQ, Ferreira SH. Hypernociceptive role of cytokines and chemokines: Targets for analgesic drug development? Pharmacol Ther 2006;112:116–138.
40. Walker AK, Kavelaars A, Heijnen CJ, Dantzer R. Neuroinflammation and comorbidity of pain and depression. Pharmacol Rev 2013;66:80–101.
41. Slade GD, Conrad MS, Diatchenko L, et al. Cytokine biomarkers and chronic pain: Association of genes, transcription, and circulating proteins with temporomandibular disorders and widespread palpation tenderness. Pain 2011;152:2802–2812.
42. Woda A, Picard P, Dutheil F. Dysfunctional stress responses in chronic pain. Psychoneuroendocrinology 2016;71:127–135.
43. Teles RP, Likhari V, Socransky SS, Haffajee AD. Salivary cytokine levels in subjects with chronic periodontitis and in periodontally healthy individuals: A cross-sectional study. J Periodontal Res 2009;44:411–417.
44. Nie S, Zhang H, Mayer KM, et al. Correlations of salivary biomarkers with clinical assessments in patients with cystic fibrosis. PLoS One 2015;10:e0135237.
45. Wormwood KL, Aslebagh R, Channaveerappa D, et al. Salivary proteomics and biomarkers in neurology and psychiatry. Proteomics Clin Appl 2015;9:899–906.
46. Da Silva Andrade A, Gamero GH, Pereira LJ, Junqueira Zanin IC, Gavião MB. Salivary cortisol levels in young adults with temporomandibular disorders. Minerva Stomatol 2008;57:109–116.
47. Quartana PJ, Buenaver LF, Edwards RR, Klick B, Haythornthwaite JA, Smith MT. Pain catastrophizing and salivary cortisol responses to laboratory pain testing in temporomandibular disorder and healthy participants. J Pain 2010;11: 186–194.
48. Riva R, Mork PJ, Westgaard RH, Lundberg U. Comparison of the cortisol awakening response in women with shoulder and neck pain and women with fibromyalgia. Psychoneuroendocrinology 2012;37:299–306.
49. Wingenfeld K, Nutzinger D, Kauth J, Hellhammer DH, Lautenbacher S. Salivary cortisol release and hypothalamic pituitary adrenal axis feedback sensitivity in fibromyalgia is associated with depression but not with pain. J Pain 2010; 11:1195–1202.