Evaluation of IL-6 levels and +3954 polymorphism of IL-1β in burning mouth syndrome: A systematic review and meta-analysis

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Abstract
This study evaluated IL-6 salivary levels as well as the +3954 polymorphism of IL-1β in patients with burning mouth syndrome and healthy individuals, through case-control studies. This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. We conducted this research in PubMed/MEDLINE, Cochrane Library and Web of Science databases. The risk of bias was measured based in the Newcastle-Ottawa Scale. Researches with a group of patients with burning mouth syndrome and a control group in which the presence of the +3954 polymorphism of IL-1β and/ or IL-6 salivary levels through non-stimulated saliva were evaluated to detect if this interleukin concentrations are increased in patients and if the polymorphism is a risk factor for this syndrome. We identified seven studies with total of 440 participants, 229 patients with burning mouth syndrome and 211 healthy controls, ages 24-84 years old. The female gender was predominant. Patients in the majority of studies did not present increased levels of IL-6 and the +3954 polymorphism of IL-1β is not a risk factor for this syndrome. A few studies researched biomarkers in this pathology and more investigations are required not only to identify salivary levels and the polymorphism evaluated, but also other interleukins and polymorphisms in order to clarify the etiopathogenesis of this syndrome as well as for propose new diagnostic methods and treatments.

KEYWORDS
burning mouth syndrome, interleukin, polymorphism

1 | INTRODUCTION
Burning mouth syndrome (BMS) is characterized by a chronic pain, without the presence of visible clinical alterations of the oral mucosal or others systemic conditions associated. This syndrome is frequently accompanied by xerostomia and dysgeusia. The burning sensation often occurs in various sites such as tongue, palate, throat and prosthesis support areas. Burning mouth syndrome mainly affects the elderly and it is more common in women ranging from 70 to 79 years old. The epidemiology, etiology, pathophysiology and diagnostic criteria are not completely understood; therefore, it is difficult to choose a specific treatment.
Recent studies indeed have suggested that the possibility of inflammation, not seen clinically, is associated with the burning sensation and may change the levels of cytokines, contributing to the pathophysiology of BMS. Some researchers observed altered IL-6 levels in saliva of patients with the syndrome. This cytokine is pleiotropic, increases the inflammatory process and the immunological reactions.

High levels of inflammatory interleukins can explain the condition of pain, burning and inflammation in BMS. However, other studies have not identified significant results in the rise of IL-6.

Interleukin-1 (IL-1) plays a very important role in inflammatory and immune-mediated diseases. Polymorphic variations in IL-1 genes are frequent and are associated with exacerbated inflammatory response. The single nucleotide polymorphism (SNP) +3954 C/T of IL-1β is located in exon 5 rs1143634. The T allele is related to a higher production of IL-1 and it increases the inflammatory process. An association between the CT genotype, high IL-1 levels and BMS was observed in patients when compared to healthy subjects.

It is essential to identify biomarkers that may contribute to the detection of burning mouth syndrome for a better understanding of its etiology and pathogenesis. It may contribute to the formulation of new diagnostic methods and treatments. In addition, saliva is an easily collectible fluid and its use has been increasing in the diagnosis of diseases. Thus, the aims of this systematic review and meta-analysis were to evaluate IL-6 salivary levels as well as the presence of the +3954 polymorphism of IL-1β in patients with BMS and healthy individuals, through evaluating case-control studies.

2 | METHODS

2.1 | Registry protocol

The present systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist, and it was registered in the International Prospective Register of Systematic Reviews (PROSPERO), CRD 42018094563.

2.2 | Eligibility criteria

Two questions conducted this systematic review and meta-analysis based on the “population, intervention, control, and outcome” (PICO) criteria, the questions were “Are the salivary levels of IL-6 increased in Burning Mouth Syndrome?” and “Is the +3954 polymorphism of IL-1β a risk factor for the development of this disease?” Thus, in accordance with the PICO criteria, the Population was composed by patients diagnosed with burning mouth syndrome and healthy people, the Intervention was the detection of the genetic polymorphism and IL-6 salivary levels in individuals with the disease, Comparison was the presence of +3954 of IL-1β SNP and IL-6 salivary levels in healthy individuals, and the Outcomes were that SNP as a risk factor for the development of BMS and IL-6 salivary levels are exacerbated in these patients.

Case-control studies were included, researches with a group of patients with burning mouth syndrome and a control group in which the presence of the +3954 polymorphism of IL-1β and/or the salivary levels of IL-6 through unstimulated saliva were evaluated. Studies of other polymorphisms and/or interleukins, case reports, reviews, studies without the comparison of a control group, or that measured interleukin evaluated through other forms than unstimulated saliva were excluded. This criterion was used because it is not possible to compare interleukin levels from studies with different methods. The stimulation of whole saliva can change interleukin levels in BMS as it can be seen in Suh et al (2009) work. Moreover, the levels of IL-6 are not the same in blood and whole saliva in patients with inflammatory oral diseases. The same occurs in healthy people.

2.3 | Information sources and search strategy

In this study, two researchers, CPC and CAAL, conducted searches PubMed/MEDLINE, Cochrane Library and Web of Science for articles published until April 2019, following the eligibility criteria. The research terms were “Burning Mouth Syndrome Interleukin or Burning Mouth Syndrome Polymorphism or Burning Mouth Syndrome salivary levels in combination with the Boolean operator.” In addition, OpenGrey (www.opengrey.eu) was used for the research of gray literature. The studies were chosen according to the title and summary of articles.

2.4 | Data collection process

The author (CPC) collected important information in the articles, and a second author (CAAL) reviewed all the data collected. The variables collected were as follows: author, type of study, number of patients, number of healthy individuals, gender, mean age, salivary levels of IL-6 and presence of +3954 SNP of IL-1β. Another investigator analyzed the differences in choice between the researchers, and a consensus was reached through discussion.

2.5 | Risk of bias

The Newcastle-Ottawa scale (NOS) was used to assess the internal validity, risk of bias in case-control studies, which focus on blinding, outcome data and other possible bias. The NOS evaluated the quality of studies based on the selection of study groups, comparability of them and the investigation of exposure to the case-control studies through eight questions. A maximum of nine stars can be attributed to a study, corresponding to the highest quality. Five stars or less are classified as high risk of bias and six stars or more as low risk of bias. Then, the selection can provide four stars, two stars can
be allotted to the compatibility and three stars can be given for the exposure.

The diagnosis of BMS after excluding local (candidiasis, lichen planus, hyposalivation) or systemic disorders (anemia, deficiencies of vitamin B12 or folic acid, Sjögren's syndrome, diabetes) causing burning mouth sensation was done by Boras et al (2006),22 de Souza et al (2015),9 Pekiner et al (2009)8 and Kim et al (2017).23 Guimarães et al (2006)15 followed Bergdahl and Bergdahl (2007)24 criteria. All patients were examined by two dentists, and participants with oral lesions or lichenoid reactions were excluded. Patients did not present any evidence of malignancy, connective tissue, metabolic or infectious disorders, or vitamin deficiency. Simčič et al (2006)7 reported that the clinical examination was followed the standard clinical criteria and the medical, dental and social histories were collected. However, any information about the laboratory tests was provided and it can be a risk of bias. Suh et al (2009)11 did not inform any diagnostic information, and in their study, three of the patients had mild anemia, eight had diabetes under control and three were receiving female hormone replacement therapy. In the control group, four subjects had diabetes under control, and it could represent a bias in the results of this systematic review and meta-analysis.

2.6 | Summary measures

The meta-analysis was based on the inverse variance (IV) for the expression salivary levels of IL-6. These data were considered continuous outcome and evaluated using mean difference (MD) values, with mean significant difference when $P < .05$. Two studies (Souza et al./ Pekiner et al.) did not report the value of standard deviation (SD), and were not included in the meta-analysis. So, we used the Hozo method25 to calculate the SD of continuous measures when these data were not available. This method is considered useful when the authors did not report SD but the median, maximum and minimum values.26

In analysis with significant heterogeneity ($P < .10$), a random-effects model was used to assess the significance of the treatment effects. Where no statistically significant heterogeneity was found, analysis was performed using a fixed effects model.27

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**FIGURE 1** Prisma flow diagram
Software (RevMan version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2014) was used for meta-analysis.

2.7 | Additional analysis

The Kappa coefficient was used to assess the inter-reader agreement at the time of inclusion of the articles of PubMed (0.78) Web of Science (0.75) and Cochrane (1.0) in the present study.

3 | RESULTS

3.1 | Literature search

The search strategy is presented in a flow diagram (Figure 1). It was carried out in databases such as PubMed/ MEDLINE (50), Web of Science (70) and Cochrane Library (10), totaling 130 references. After the duplicates were removed, 123 studies remained, and were analyzed through the titles and summaries and inclusion and exclusion criteria. Of the total, eight studies were eligible; one of them undertaken by Kho et al (2013) was excluded because the method of collection—stimulated saliva—was different from the other studies, which worked with unstimulated saliva. Thus, seven articles were included in this systematic review: Boras et al (2006); Simčič et al (2006); Guimarães et al (2006); Suh et al (2009); Pekiner et al (2009); de Souza et al (2015); and Kim et al (2017).

3.2 | Description of the studies

Details about the seven studies included in this systematic review were described in (Table 1). All are case-control studies that measured IL-6 salivary levels or detected the presence of +3954 IL-1β polymorphism. A total of 229 patients—210 females and 19 males—were evaluated. Their ages ranged from 25 to 80 years. The control group consisted of 211 subjects, 190 females, 21 males and their age ranged from 24 to 84 years old. The period of duration of their illness, from time of diagnosis, was 10 days to 30 years according to the evaluated data.

3.3 | Quality assessment and risk of bias of studies included

The risk of bias was analyzed through the NOS (Figure 2). Two studies did not report how long the cases had the disease. According to this criteria, Boras et al (2006) and Suh et al (2009) have seven stars, Kim et al (2017) and Simčič et al (2006) have eight stars and Guimarães et al (2006); Pekiner et al (2009) and de Souza et al (2015) have nine stars.

3.4 | Expression salivary levels of IL-6

Salivary levels of interleukin 6 were evaluated in five studies through unstimulated saliva and they are expressed by mean ± SD (Table 2). Some studies found higher IL-6 salivary levels in the group of patients in comparison with healthy control individuals. Nevertheless, there was no association between BMS and IL-6 concentrations in the other studies.

In quantitative analysis, although the expression salivary levels of IL-6 was higher for experimental groups, there was no significant difference when these were compared with control groups (P = .09; MD: 11.72; 95% CI: −1.65 to 25.09; heterogeneity: P < .00001; I²: 98%) (Figure 3).

3.5 | The presence of SNP +3954 da IL-1β

The evaluation of the presence of +3954 polymorphism of IL-1β was performed by two studies (Table 3). In the first one, there is no association between BMS and the polymorphism +3954 da IL-1β. The

<table>
<thead>
<tr>
<th>Variables</th>
<th>Gender Patients (female/male)</th>
<th>Gender Controls (female/male)</th>
<th>Mean Age Patients</th>
<th>Mean Age Controls</th>
<th>Duration of BMS in patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al, 2017</td>
<td>40 (40/0)</td>
<td>40 (40/0)</td>
<td>62 ± 10</td>
<td>61.7 ± 10.5</td>
<td>2-150 mo</td>
</tr>
<tr>
<td>Guimarães et al, 2006</td>
<td>31 (26/5)</td>
<td>31 (26/5)</td>
<td>55.7 (25-79)</td>
<td>50.2 (24-84)</td>
<td>At least 6 mo</td>
</tr>
<tr>
<td>Suh, 2009</td>
<td>40 (40/0)</td>
<td>20 (20/0)</td>
<td>61.6 ± 10.1</td>
<td>65.1 ± 9.0</td>
<td>34.2 mo (10 d-30 y)</td>
</tr>
<tr>
<td>Pekiner et al, 2009</td>
<td>30 (19/11)</td>
<td>30 (21/9)</td>
<td>54.3 ± 12.78</td>
<td>50.7 ± 6.23</td>
<td>At least 6 mo</td>
</tr>
<tr>
<td>Boras et al, 2006</td>
<td>28 (28/0)</td>
<td>28 (28/0)</td>
<td>64.05 (48-80)</td>
<td>63.82 (40-75)</td>
<td>Not informed</td>
</tr>
<tr>
<td>Simčič et al, 2006</td>
<td>30 (28/2)</td>
<td>30 (24/6)</td>
<td>(55-65)</td>
<td>(55-65)</td>
<td>Not informed</td>
</tr>
<tr>
<td>de Souza et al, 2015</td>
<td>30 (29/1)</td>
<td>32 (31/1)</td>
<td>62.13 ± 12.74</td>
<td>61.59 ± 12.84</td>
<td>37.23 ± 40.48</td>
</tr>
</tbody>
</table>
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evaluated distributions in patients were (TT:CT:CC, 0:2:38) while the controls were (TT:CT:CC, 0:0:40). However, p value was not significant ($X^2 = .494$).

In the second research, a significant increase in the IL-1 high production genotype CT was observed in the group with BMS ($P = X^2 = < .005$). The distribution of IL-1 genotypes in the case group

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients BMS genotype</th>
<th>Controls genotype</th>
<th>Patients BMS alleles</th>
<th>Controls alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al, (2017)</td>
<td>CC 38</td>
<td>CT 2</td>
<td>TT 0</td>
<td>0.494</td>
</tr>
<tr>
<td>Guimarães et al, (2006)</td>
<td>CC 9</td>
<td>CT 22</td>
<td>TT 0</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Note: $P = X^2$
was (TT:CT:CC, 0:22:9) while in the control group was (TT:CT:CC, 0:22:9).15

4 | DISCUSSION

This systematic review and meta-analysis included articles which analyzed IL-6 salivary levels through unstimulated saliva and/or the presence of the IL1β +3954 polymorphism in patients with burning mouth syndrome, comparing their results with a control group. A total of 229 patients were evaluated, 210 females and 19 males, ages ranged from 24 to 84 years old. The prevalence of the disease in females, especially after menopause, is reported by several studies.3,16,28-31

There was no association between patients with BMS and IL-6 levels in comparison with healthy controls, in most of studies. However, it is necessary to conduct more case-control researches to confirm the first hypothesis which stated that levels of IL-6 would be exacerbated in patients with the disease. Elevated IL-6 concentrations were observed in patients analyzed by Simčić et al (2006)7 and de Souza et al (2015),3 however Suh et al (2009),11 Boras et al, (2009)22 and Pekiner et al (2009)9 did not find differences between patients and controls.

Raised IL-6 concentrations may predispose to a greater inflammation state and, consequently, accentuated burning mouth syndrome manifestation. Furthermore, interleukins can be important biomarkers for the diagnosis of this disease because no oral mucosal abnormalities were detected.

All studies used ELISA kits, nevertheless Suh et al (2009)11 used a multiplex assay kit (LINCO Research) to determine the levels of IL-6. A multiplex assay is a derivative of an ELISA, it has a high accuracy in interleukin detection, and it can influence the results.32

An increase in IL-6 production was found in women with osteoporosis and a reduction of estrogen.33 A recent study with post-menopausal female with osteoporosis illustrated that the reduction of estradiol concentration causes a rise in the activity of IL-1β, IL-6 and TNF-α,34 and it could happen with patients in the studies. Some polymorphisms are associated with the IL-6 gene, one of them is −174 G/C rs1800795 that is located in promoter region.35 This polymorphism affects the constitutive transcription of the interleukin gene by controlling the production.36 G replaces C and the C allele has a protective function because it is associated with a lower secretion of IL-6.37 The CC homozygous causes a lower production of IL-6.38 The possible presence of this polymorphism in these patients could also explain the different results in the studies.

The polymorphism −572 C/G IL-6 rs1800796 is located in the promoter region and can cause an abnormality of expression of this interleukin.39 The genetic polymorphisms of IL-6 modify its production, their presence can vary in the same population and between populations. To our knowledge, until the present moment, there are no researches that evaluated IL-6 polymorphisms in patients with BMS. It is required because they can be used as diagnostic biomarkers for this syndrome.

A study evaluated the polymorphism +3954 C/T IL1β and found the CT genotype in 71% patients while only 31.3% control subjects presented this genotype; 29% patients had CC, nevertheless 68.7% healthy individuals exhibited CC genotype.15 The T allele is related to an exacerbated production of IL-1, consequently it raises the inflammatory process.14 The analyzed polymorphism had also an association with chronic periodontal diseases.40,41 However, other study23 did not observe the same results because 95% of patients had CC, 5% were CT, and 100% of controls presented CC.

There is a possibility that the difference between the researchers evaluated in this systematic review occurred because one study was conducted with Korean individuals22 and other15 was carried out in Brazil and had no information about ethnicity, which is mixed in this country. Probably, the participants of these researchers were genetically distinct. The polymorphisms vary according to the ethnicity.42

Further research, including different populations, is needed. The IL-1 family of cytokines has been targeting by many researches in order to discover a therapeutic for patients with inflammatory diseases.43 If +3954 C/T IL1β and/or higher levels of IL-1 are present in patients with BMS, they can be relevant biomarkers, which may cause not only greater inflammation, but also aggravate BMS.

The use of biomarkers can provide a precise diagnosis, as well as a specific therapy. Tocilizumab can block IL-6 receptor reducing its activity. This drug can be effective in several inflammatory diseases and it is already used in rheumatoid arthritis patients44,45 and anakinra, canakinumab and rilonacept which are already approved to treated inflammatory diseases, reducing IL-1 levels.46 Until now, there is no studies with these drugs in burning mouth syndrome. It is important to evaluate other biomarkers in this syndrome like TNF-α, NF-kB, IL-1α, IL-2, IL-4, IL-8, IL-10, MCP-1, PGE2 because they can have a therapeutic value.

5 | CONCLUSION

Some studies presented that there are increased levels of IL-6 in burning mouth syndrome. There is no evidence to suggest that the +3954 IL1β polymorphism can be considered a risk factor for the disease as there were only two studies on this topic with 132 patients. The analysis of this polymorphism has demonstrated a great divergence among the studies. However, there are a few studies with biomarkers in BMS. It is paramount to propose future researches, not only to measure the IL-6 salivary concentrations and the polymorphism analyzed, but also to identify possible changes in other biomarkers such as pro- and anti-inflammatory interleukins and their polymorphisms that can be associated with BMS. It is important for the establishment of a precise diagnosis, which will also contribute for a specific treatment.

ACKNOWLEDGEMENTS

Camilla Porto Campello received a scholarship from Coordenação de Aperfeiçoamento de Pessoal de Nivel Superior—Brasil (CAPES)—Finance Code 001 during her PhD. Belmiro Cavalcanti do Egito Vasconcelos is a CNPq productivity fellow.
CONFLICT OF INTEREST
The authors declare that they have no conflicts of interest.

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**How to cite this article:** Campello CP, Pellizzer EP, Vasconcelos BCDE, Moraes SLD, Lemos CAA, Muniz MTC. Evaluation of IL-6 levels and +3954 polymorphism of IL-1β in burning mouth syndrome: A systematic review and meta-analysis. *J Oral Pathol Med*. 2020;00:1–8. [https://doi.org/10.1111/jop.13018](https://doi.org/10.1111/jop.13018)
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