Abstract: Objective: This research aims to analyze the available specialized literature concerning the association between Herpesviruses [Cytomegalovirus (CMV), Epstein Barr virus (EBV), Herpes Simplex virus (HSV)] and chronic periodontitis to clarify the possible role of these microorganisms in the progression and severity of the disease. Materials and Methods: A search for scientific articles was carried out in March 2019 in the main metasearch engines: PubMed /MEDLINE, SciELO, EBSCO, and the Trip search engine, to select articles according to the exclusion and inclusion criteria. The analysis of the articles was carried out through a data matrix expressed in frequency tables using descriptive statistics with measures of central tendency, dispersion, and correlation. Results: The results of this study show that the presence of CMV, EBV, and HSV in patients with chronic periodontitis is related to an increase in clinical parameters such as probing pocket depth (PD), clinical insertion loss (CIL) and bleeding on probing (BOP), in 96%, 60% and 40% of the studies, respectively, for CMV; 96.55% (PD), 51.72% (CIL), and 48.28% (BOP) for EBV, and 80% (PD), 90% (CIL), and 60% (BOP) for HSV. The average prevalence of EBV, CMV, and HSV was 46.3%, 35.4%, and 40.1%, respectively. Conclusions: EBV, CMV, and HSV could be associated with the progression and severity of periodontal disease as they are related to a greater probing depth, greater clinical insertion loss, and greater bleeding on probing. EBV presented a higher prevalence in the reviewed literature. More clinical studies are needed to verify a direct relationship between EBV, HSV, CMV, and periodontal disease, to confirm the trends observed in this work. Keywords: Cytomegalovirus, Epstein-Barr virus, herpes simplex virus, periodontitis, prevalence, periodontal pocket.
INTRODUCTION.
Chronic periodontitis has been described as one of the most prevalent microbial inflammatory diseases worldwide. It destroys the supporting tissues of the tooth, including the periodontal ligament, alveolar bone, and gingival tissues.¹

Although different studies confirm that the presence of bacterial complexes is necessary and indispensable for the onset and progression of this disease, other studies report that the mere presence of periodontopathogenic bacteria in oral tissues is not sufficient to cause and spread this pathology.²

A number of studies suggest that the onset and progression of periodontitis are influenced by multiple factors, and although periodontal disease has been reported to be multifactorial and of immunoinflammatory origin,³ the role of other microorganisms in its pathogenesis -in addition to bacteria- is still unclear.

Consequently, the herpes virus has been proposed as a putative pathogen in periodontal disease.² It is thus suggested that this microorganism plays an active role in the progression of this pathology, either initiating or accelerating periodontal destruction through different viral mechanisms.⁴

The aim of this study is to carry out a critical literature review concerning the role of other microorganisms, specifically herpes viruses, involved in the pathogenesis of periodontal disease, its progression and severity in adult and systemically healthy patients.

MATERIALS AND METHODS.
This review was carried out following the PRISMA5 guide.

Literature Review
The search strategy involved the biomedical databases: PubMed, SciELO, EBSCO, and the Trip search engine, and a manual search in periodontics journals such as: Periodontology 2000, Journal of Clinical Periodontology and Journal of Periodontology published in the last 10 years, until December 2019, using the following keywords: Herpes virus AND periodontitis OR Herpes virus AND chronic periodontitis NOT aggressive OR EBV AND chronic periodontitis OR HCMV AND chronic periodontitis OR HVS AND chronic periodontitis.

The discrimination criteria between studies, for validity and relevance of the research, were as follows:
- Studies carried out from the year 2000 onwards, due to the change made in the classification of periodontal diseases in the 1999 workshop.
- Studies conducted in adult humans.

Selection criteria
Inclusion criteria
- Articles reporting systemically healthy adult patients with chronic periodontitis.
- Articles that related the presence of viruses and chronic periodontitis.
- Articles including one or more of the following variables in their study: presence of Herpes Simplex Virus type I (HSV), Human Cytomegalovirus (CMV), Epstein Barr virus (EBV).

Exclusion criteria
- Articles published in non-indexed journals.
- Articles that included pregnant women.
- Articles that included smokers.
- Articles that included patients who received antiviral and/or antibiotic treatment during the 3 months preceding the study.
- Articles that included patients who received periodontal treatment during the 3 months preceding the study.

Results:
The prevalence of EBV, CMV, and HSV were 90% (PD), 51% (CIL) and 48% (BOP) respectively, in the 96%, 60% and 40% of the studies, for HCMV; 96.55% (PD), 51.72% (CIL) and 48.28% (BOP) for EBV; and 60% (BOP) for HSV. The prevalence of EBV, CMV, and HSV was 46.3%, 35.4%, and 40.1%, respectively.

Conclusion:
The EBV, CMV, and HSV could be associated with the progression and severity of periodontal disease, due to their association with a greater probing depth, greater attachment loss, and greater bleeding on probing.

The EBV presented a higher prevalence in the reviewed literature. More clinical studies are needed to verify a direct relationship between EBV, HSV, CMV and periodontal disease, to confirm the trends observed in this study.

Keywords:
Citomegalovirus; virus epstein-barr; virus herpes simplex; prevalence; periodontitis; bolsa periodontal.

Analysis of results
Variables considered in the data matrix (Annex I) were analyzed qualitatively and quantitatively, as appropriate. However, in some, triangulation was used that mixed qualitative and quantitative data. A descriptive statistical analysis was carried out using the measures of central tendency, dispersion, and correlation.

Table 1. Description of reviewed studies evaluating association between both variables.

<table>
<thead>
<tr>
<th>Publication</th>
<th>Year</th>
<th>Study design</th>
<th>Sample size</th>
<th>Type of samples technique</th>
<th>Sample extraction</th>
<th>PCR type</th>
<th>EBV</th>
<th>HSV</th>
<th>CMV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hernández et al.</td>
<td>2016</td>
<td>Case-control study</td>
<td>11</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>17</td>
<td>27</td>
<td>*</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>2007</td>
<td>Case-control study</td>
<td>143</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>63.6</td>
<td>*</td>
<td>79</td>
</tr>
<tr>
<td>Shah et al.</td>
<td>2016</td>
<td>Case-control study</td>
<td>40</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>25</td>
<td>37</td>
<td>*</td>
</tr>
<tr>
<td>Kazi et al.</td>
<td>2015</td>
<td>Cross-sectional study</td>
<td>75</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Multiple</td>
<td>37.33</td>
<td>28</td>
<td>30.66</td>
</tr>
<tr>
<td>Kato et al.</td>
<td>2013</td>
<td>Case-control study</td>
<td>85</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>66</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Das et al.</td>
<td>2012</td>
<td>Case-control study</td>
<td>10</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Multiple</td>
<td>32</td>
<td>76</td>
<td>28</td>
</tr>
<tr>
<td>Botero et al.</td>
<td>2007</td>
<td>Case-control study</td>
<td>20</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>*</td>
<td>*</td>
<td>60</td>
</tr>
<tr>
<td>Imbronito et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>40</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>46.7</td>
<td>40</td>
<td>50</td>
</tr>
<tr>
<td>Bilder et al.</td>
<td>2013</td>
<td>Case-control study</td>
<td>59</td>
<td>Stimulated saliva</td>
<td>Plastic tubes</td>
<td>Real-time</td>
<td>40</td>
<td>5</td>
<td>15</td>
</tr>
<tr>
<td>Saygun et al.</td>
<td>2002</td>
<td>Case-control study</td>
<td>30</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>16.7</td>
<td>6.7</td>
<td>44.3</td>
</tr>
<tr>
<td>Li Ying et al.</td>
<td>2004</td>
<td>Case-control study</td>
<td>62</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>58</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Ling et al.</td>
<td>2004</td>
<td>Cross-sectional study</td>
<td>20</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>15</td>
<td>50</td>
<td>75</td>
</tr>
<tr>
<td>Tantivanich et al.</td>
<td>2004</td>
<td>Case-control study</td>
<td>50</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>*</td>
<td>*</td>
<td>8</td>
</tr>
<tr>
<td>Idesawa et al.</td>
<td>2004</td>
<td>Cross-sectional study</td>
<td>33</td>
<td>Stimulated saliva</td>
<td>Plastic tubes</td>
<td>Real-time</td>
<td>48.5</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Klemen et al.</td>
<td>2005</td>
<td>Cross-sectional study</td>
<td>66</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>44</td>
<td>*</td>
<td>3</td>
</tr>
<tr>
<td>Konstantinidis et al.</td>
<td>2005</td>
<td>Case-control study</td>
<td>22</td>
<td>Gingival crevice</td>
<td>Paper points</td>
<td>Real-time</td>
<td>55</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Wu et al.</td>
<td>2006</td>
<td>Case-control study</td>
<td>65</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>66</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Moghim et al.</td>
<td>2007</td>
<td>Cross-sectional study</td>
<td>61</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Nested</td>
<td>60.7</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Saygun et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>15</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Real-time</td>
<td>60</td>
<td>53</td>
<td>*</td>
</tr>
<tr>
<td>Rotola et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>24</td>
<td>Gingival tissue</td>
<td>Biopsy</td>
<td>Nested</td>
<td>50</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Combs et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>13</td>
<td>Subgingival biofilm / Saliva</td>
<td>Curettes</td>
<td>Real-time</td>
<td>*</td>
<td>*</td>
<td>8.8</td>
</tr>
<tr>
<td>Chalabi et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>80</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Nested</td>
<td>72.5</td>
<td>50</td>
<td>*</td>
</tr>
<tr>
<td>Nishiyama et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>50</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Nested</td>
<td>*</td>
<td>46.4</td>
<td>*</td>
</tr>
<tr>
<td>Botero et al.</td>
<td>2008</td>
<td>Case-control study</td>
<td>37</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>*</td>
<td>*</td>
<td>80</td>
</tr>
<tr>
<td>Chalabi et al.</td>
<td>2010</td>
<td>Case-control study</td>
<td>40</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Nested</td>
<td>72.5</td>
<td>50</td>
<td>*</td>
</tr>
<tr>
<td>Grenier et al.</td>
<td>2009</td>
<td>Case-control study</td>
<td>31</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>3</td>
<td>13</td>
<td>35</td>
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<tr>
<td>Dawson et al.</td>
<td>2009</td>
<td>Cross-sectional study</td>
<td>65</td>
<td>Saliva Plastic tubes</td>
<td>Real-time</td>
<td>82</td>
<td>*</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bilichodmat et al.</td>
<td>2009</td>
<td>Case-control study</td>
<td>19</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Multiple</td>
<td>78</td>
<td>100</td>
<td>26</td>
</tr>
<tr>
<td>Sharma et al.</td>
<td>2012</td>
<td>Case-control study</td>
<td>20</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Nested</td>
<td>25</td>
<td>*</td>
<td>20</td>
</tr>
<tr>
<td>Tomasini et al.</td>
<td>2012</td>
<td>Case-control study</td>
<td>20</td>
<td>Periodontal pocket</td>
<td>Biopsy</td>
<td>Nested</td>
<td>*</td>
<td>30</td>
<td>*</td>
</tr>
<tr>
<td>Vincent-Bugnas et al.</td>
<td>2013</td>
<td>Cross-sectional study</td>
<td>20</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Real-time</td>
<td>13</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Petrovic et al.</td>
<td>2014</td>
<td>Case-control study</td>
<td>36</td>
<td>Gingival crevicular fluid</td>
<td>Paper points</td>
<td>Nested</td>
<td>*</td>
<td>38.9</td>
<td>*</td>
</tr>
<tr>
<td>Kato et al.</td>
<td>2015</td>
<td>Case-control study</td>
<td>25</td>
<td>Subgingival biofilm</td>
<td>Paper points</td>
<td>Real-time</td>
<td>68</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Khosropanaha et al.</td>
<td>2015</td>
<td>Case-control study</td>
<td>75</td>
<td>Saliva/Gingival tissue</td>
<td>Paper points</td>
<td>Real-time</td>
<td>51.3</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>Kazi et al.</td>
<td>2017</td>
<td>Case-control study</td>
<td>300</td>
<td>Subgingival biofilm</td>
<td>Curettes</td>
<td>Multiples</td>
<td>30.6</td>
<td>46.6</td>
<td>19.3</td>
</tr>
</tbody>
</table>

*: Not available. EBV: Epstein-Barr Virus. HSV: Herpes Simplex virus type 1. CMV: Cytomegalovirus.
Table 2. Statistical analysis of the sample.

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Patients</th>
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</thead>
<tbody>
<tr>
<td>Lowest</td>
<td>10</td>
</tr>
<tr>
<td>1st Qu</td>
<td>21.5</td>
</tr>
<tr>
<td>Median</td>
<td>34.5</td>
</tr>
<tr>
<td>Mean (Average)</td>
<td>42.8</td>
</tr>
<tr>
<td>3rd Qu</td>
<td>62.7</td>
</tr>
<tr>
<td>Highest</td>
<td>300</td>
</tr>
<tr>
<td>Standard Deviation (SD)</td>
<td>26.8</td>
</tr>
</tbody>
</table>

Table 3. Relationship between the presence of CMV and an increase in periodontopathogens, proinflammatory cells, enzymes (MMP), proinflammatory cytokines and clinical parameters.

<table>
<thead>
<tr>
<th>Total number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of studies that analyzed the virus</td>
</tr>
<tr>
<td>Frequency</td>
</tr>
<tr>
<td>39</td>
</tr>
</tbody>
</table>

| Periodontopathogens | Treponema denticola | 0 | 0 |
| Porphyromonas gingivalis | 7 | 28 |
| Tannerella forsythia | 4 | 16 |
| Aggregatibacter actinomycetemcomitans | 0 | 0 |
| Fusobacterium nucleatum | 0 | 0 |
| Porphyromonas nigrescens | 1 | 4 |
| Prevotella intermedia | 2 | 8 |
| Porphyromonas gingivalis | 7 | 28 |
| Parrus ginvialis | 10 | 40 |
| Tannerella forsythia | 4 | 16 |
| Aggregatibacter actinomycetemcomitans | 0 | 0 |
| Fusobacterium nucleatum | 0 | 0 |
| Porphyromonas nigrescens | 1 | 4 |
| Prevotella intermedia | 2 | 8 |
| Cells | B lymphocytes | 2 | 8 |
| T lymphocytes | 10 | 40 |
| Macrophages | 11 | 44 |
| PMN | 5 | 20 |
| Osteoclasts | 1 | 4 |
| Enzymes | Metalloproteinases | 1 | 4 |
| Proinflammatory cytokines | IL-1 | 4 | 16 |
| IL-6 | 2 | 8 |
| IL-10 | 0 | 0 |
| IL-4 | 1 | 4 |
| TNF-α | 4 | 16 |
| Clinical parameters | Probing depth | 24 | 96 |
| Clinical insertion loss | 15 | 60 |
| Gingival bleeding | 10 | 40 |

RESULTS.
Selection of studies
A total of 965 studies were identified in an initial search stage. Of these, 655 were selected when applying the first filter (adult patients). After the second filter, 475 publications were obtained. Of these, titles and abstracts were analyzed, resulting in 288 studies. Finally, 39 publications that met the inclusion and exclusion criteria were selected, which were fully analyzed (Table 1).
Table 4. Relationship between the presence of HSV and an increase in periodontopathogens, proinflammatory cells, enzymes (MMP), proinflammatory cytokines and clinical parameters.

<table>
<thead>
<tr>
<th>Total number of studies</th>
<th>39</th>
<th>Number of studies that analyzed the virus</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periodontopathogens</td>
<td>Treponema denticola</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Porphyromonas gingivalis</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Tannerella forsythia</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Aggregatibacter actinomycetemcomitans</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Fusobacterium nucleatum</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Porphyromona nigrescens</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Prevotella intermedia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cells</td>
<td>B lymphocytes</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>T lymphocytes</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>PMN</td>
<td>3</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>Osteoclasts</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Metalloproteinases</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Proinflammatory cytokines</td>
<td>IL-1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IL-6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IL-10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>IL-4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>TNF-α</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td>Probing depth</td>
<td>8</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Clinical insertion loss</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>Gingival bleeding</td>
<td>6</td>
<td>60</td>
</tr>
</tbody>
</table>

Characteristics of the studies

The minimum sample analyzed corresponds to 10 patients, the first quartile corresponds to 21.5; the median to 34.5; the mean to 42.88; the third quartile to 62.75; a maximum sample value of 300 patients, with the standard deviation of 26.83 (Table 2).

It is also possible to observe an atypical point, a value that is far from the sample average, and which is represented by the 300 patients included in one study.99

Relationship between CMV and an increase in periodontopathogens, proinflammatory cells, metalloproteinase enzymes (MMP), proinflammatory cytokines and clinical parameters.

Of the 39 publications analyzed (Table 3), 25 reported the presence of CMV in patients with chronic periodontitis, associating the virus with an increase in the number of Porphyromonas gingivalis (28%), Tannerella forsythia (16%), T lymphocytes (40%), macrophages (44%), polymorphonuclear neutrophils (PMN) (20%), IL-1 and tumor necrosis factor-α (TNF-α) (16%).

Furthermore, it was associated with an increase in clinical parameters such as probing depth, clinical insertion loss, and gingival bleeding, in 96%, 60%, and 40% of the studies, respectively.

Relationship between HSV and an increase in periodontopathogens, proinflammatory cells, enzymes (MMP), proinflammatory cytokines and clinical parameters.

Regarding HSV, 10 studies found the presence of this virus in periodontal tissues, associating it with an increase of 10% in Porphyromonas gingivalis (Pg), Treponema denticola (Td) and Tannerella forsythia (TF); PMN (30%), B lymphocytes (20%), T lymphocytes and macrophages (50%). An increase was observed in clinical parameters, with clinical insertion loss being the most prevalent (90%), followed by probing depth (80%), and gingival bleeding (60%) (Table 4).

Relationship between EBV and an increase in periodontopathogens, proinflammatory cells, enzymes (MMP), proinflammatory cytokines and clinical parameters.

Twenty-nine studies reported a relationship between this virus and periodontal disease. Regarding periodontopathogens, 24.14% of the articles reviewed reported a relationship between the presence of this virus and an increase in Pg; and 13.79%
Table 5. Relationship between EBV and the increase in periodontopathogens, proinflammatory cells, enzymes (MMP), proinflammatory cytokines and clinical parameters.

<table>
<thead>
<tr>
<th>Total number of studies</th>
<th>39</th>
<th>Number of studies that analyzed the virus</th>
<th>29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td></td>
<td>CMV %</td>
<td></td>
</tr>
<tr>
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<td>24.14</td>
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<tr>
<td>Tannerella forsythia</td>
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<td>13.79</td>
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<tr>
<td>Aggregatibacter actinomycetemcomitans</td>
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<td>3.45</td>
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<tr>
<td>Fusobacterium nucleatum</td>
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<td>T lymphocytes</td>
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<td>Clinical parameters</td>
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<td>Probing depth</td>
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<td>Clinical insertion loss</td>
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<td>51.72</td>
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<tr>
<td>Gingival bleeding</td>
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<td>48.28</td>
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Table 6. Spearman’s correlation coefficient between EBV, HSV, and CMV.

<table>
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<th>COR(X)</th>
<th>EBV</th>
<th>HSV</th>
<th>CMV</th>
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<tr>
<td>EBV</td>
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<td>0.70</td>
<td>-0.27</td>
</tr>
<tr>
<td>HSV</td>
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<td>1.00</td>
<td>-0.05</td>
</tr>
<tr>
<td>CMV</td>
<td>-0.27</td>
<td>-0.05</td>
<td>1.00</td>
</tr>
</tbody>
</table>

associated with an increase in Tf. The percentage regarding B lymphocytes was 51.72%, and 13.79% for T lymphocytes and PMN.

For proinflammatory cytokines IL-1 and TNF-α, 10.34% of the studies suggested a relationship between the two parameters. In relation to an increase in probing depth, clinical insertion loss, and gingival bleeding, 96.55%, 51.72%, and 48.28% of the studies reported on this, respectively (Table 5).

**Correlation between EBV, HSV, and CMV**

Of the studies analyzed, eleven reported simultaneously the presence of EBV, HSV, and CMV viruses. A relationship between EBV and HSV is observed with a correlation value of 0.7 (Table 5).

There is an inverse although weak relationship between EBV and CMV (-0.27). There is practically no correlation between CMV and HSV since the indicator is very close to zero.

**DISCUSSION.**

Although bacterial presence, specifically Gram-negative species, is essential for the onset and progression of periodontal disease, it fails to fully explain it. Because of this, the participation of other microorganisms has been suggested, specifically herpes virus, in the etiology and pathogenesis of the disease.

In this regard, Shah et al. detected the presence of this virus in 96.7% of patients diagnosed with chronic...
Association between chronic periodontitis and herpes viruses: A review of the literature.


periodontitis, a percentage similar to that described by Kazi et al.,12 where the presence of the Herpes virus was observed in 81.33% of the cases. Both studies suggested a possible role of this virus in periodontal disease. Likewise, Hernández et al.,2 establish that, although the presence of HSV, CMV, and EBV is not the direct etiologic factor of periodontal disease, they can aggravate its course and prognosis.

Concerning bacterial etiology and its relationship to the presence of EBV, CMV and HSV viruses, it is described that, by means of receptors on their surface, these viruses promote bacterial colonization and aggregation of subgingival periodontopathogens.13 This infection produces the expression of inflammation mediators such as interleukin-1β (IL-1β), TNF-α, monocytes, and macrophages. Interleukin-1β and TNF-α, stimulate matrix metalloproteinases, affecting the synthesis of metalloproteinase inhibitors and therefore exacerbating periodontal bone destruction.13 Some authors suggest that these bacteria associated with viruses could increase the progression and severity of periodontal disease.14-16

In this regard, Kato et al.,17 point out that patients who present a co-infection of EBV and Porphyromonas gingivalis have a higher risk of suffering from an increase in bone destruction, compared to patients who did not present this interaction. These results agree with those obtained in this study, in which 24.14% of the articles analyzed propose a relationship between Porphyromonas gingivalis and EBV.

The results obtained in this review, regarding the presence of EBV in patients with chronic periodontitis, show a higher prevalence of this virus compared to HSV and CMV (mean of 46.3%, 40.1%, and 35.5%, respectively). These percentages are in agreement with those reported by Kazi et al.,12 in which the Epstein Barr virus was detected regardless of the severity of periodontitis. Das et al.,18 evidenced similar results, demonstrating that EBV was also significantly present in patients with chronic periodontitis (32%), compared to 8% in the control group, who were periodontally healthy. Conversely, one study found no association between the presence of EBV and the progression of periodontal disease.16,19

In parallel, Saygun et al.,20 conclude that CMV has a higher prevalence than EBV and HSV in patients with the disease, unlike what was found in this review. This discrepancy could be due, among other variables, to the different number of samples considered in both reviews. Other studies associated the presence of this virus with an increase in clinical parameters, particularly an increase in probing depth.16

This is reported by Kato et al.,17 who suggest that there is a correlation between EBV and Porphyromonas gingivalis in the formation of deep periodontal pockets.

Regarding the prevalence of CMV, this virus could increase the severity of periodontitis.23 Although the present study did not obtain significant results for the presence of Porphyromonas intermedia together with CMV as it was found only in 8% of the analyzed literature, periodontopathogens such as Porphyromonas gingivalis (28%) and Tannerella forsythia (16%) stand out. These findings are consistent with those of Imbronito et al.,24 suggesting that CMV and Tannerella forsythia coinfection is more prevalent in patients with chronic periodontitis than in periodontally healthy individuals.14-27

Regarding HSV, Kazi et al.,12 detected the presence of HSV-1 and HSV-2 in patients with severe chronic periodontitis, reporting a prevalence of HSV-1 in 52% of the cases, and HSV-2 in 56%. In this review, HSV was the virus least studied in the articles, being found only in 10 publications, although, paradoxically, it has a prevalence of 40%.

This high prevalence may be due to the number of studies dedicated to the different viruses, since the number of articles for CMV and EBV was higher than for HSV, which would explain this result.

HSV could be associated with greater severity and progression of periodontal disease.18 In this regard, the observations made in this study suggest a relationship between this virus and the increase in clinical parameters of probing depth, clinical insertion loss and bleeding on probing (80%, 90%, and 60%, respectively). It should be noted again that, although the percentages are high, these could be affected by sample size, since there were only 10 studies that related this virus to the disease.

Regarding CMV, a number of different studies support the presence and role of this virus in periodontal disease.11,25 It infects different cell types and can undergo latency in the progenitor cells of macrophages, monocytes and Tannerella lymphocytes.31,16

This virus shows a marked tropism for cells of the immune system and interferes with the innate, adaptive
cellular and humoral immune response through the activation and silencing of natural killer (NK), decreasing and altering the presentation of MHC I and II complex antigens, thus interfering with apoptosis. \(^8\)

Likewise, it affects PMNs by inducing abnormalities in their adherence, chemotaxis, phagocytosis, oxidative processes, secretors, and bactericidal activity, and is capable of deterring the powerful response of antiviral cytokines and even interfere with their production. \(^9\)

Other studies comparing the detection of herpes virus with clinical parameters, including probing depth and clinical insertion loss, report the presence of CMV in more than 50% of the affected sites in patients with chronic periodontitis, showing a lower frequency of the virus in periodontally healthy sites. \(^24\) In this regard, this review obtained similar results, observing an increase in probing depth, clinical insertion loss, and bleeding on probing in most of the studies, with percentages of 96%, 60%, and 40%, respectively.

These viruses are capable of infecting and altering PMNs, macrophages, and lymphocytes, thus being able to play a role in the pathogenesis of chronic periodontitis. Thus, the reactivation of CMV and EBV in periodontitis could be associated with the progression of this disease. \(^9\)

A meta-analysis obtained similar results when concluding that a simultaneous infection by EBV (B lymphocytes) and HSV or CMV (T lymphocytes and macrophages) could exert an additional or synergistic pathogenic effect on periodontal tissues. \(^8\)

There is a high frequency of association between EBV and an increase in B lymphocytes, as well as an increase in IL-1 and TNF-α, proinflammatory cytokines that may contribute to the progression and severity of the disease. \(^11,16\)

The results obtained in this review show an increase in B lymphocytes, T lymphocytes, PMN, macrophages, IL-1 and TNF-α in response to the presence of these viruses, which would partially explain the increase in clinical parameters in periodontal disease. Various authors point out that these viruses have a direct effect on fibroblasts, keratinocytes, and inflammatory cells. \(^12,22,24,25\) It is suggested that as a result of the replication of lymphocytes, PMNs, and macrophages, viruses can adjust themselves to the defense mechanisms of the immune system and influence the host response. Likewise, they could reduce the capacity of periodontal tissues by altering structural cells or defensive cells of the periodontium. \(^22\)

Consequently, periodontitis could be exacerbated by a herpes virus-bacteria co-infection. \(^17,28,29\) This is why it has been suggested that the pathogenesis of periodontitis involves multiple events consisting of complex interactions between herpes viruses, bacterial complexes, and host factors. \(^15\)

Finally, the correlation between the different viruses was analyzed, resulting in a correlation value of 0.7 for EBV and HSV (Table 6). This implies a synergistic relationship in their various periods of activity, favoring the release of viral proteins, triggering their productive phase and, therefore, enhancing their direct relationship. \(^10\)

On the other hand, no correlation was found between CMV and HSV viruses, as such, if one of these viruses increases its activity due to various conditions, it does not necessarily imply a direct effect on the other. This finding is relevant when conducting experimental studies, since it is recommended to take into account both EBV and HSV within their variables and how these can influence host response.

It should be noted that this research has some limitations, such as the lack of statistically significant evidence supporting the relationship between the presence of the different viruses and the severity and progression of periodontal disease.

Secondly, the different ways of sampling used in the studies included gingival crevicular fluid, biopsies of periodontal tissue, subgingival plaque, and saliva. They may have different biases, since even manipulation could alter the results.

Finally, this study, being descriptive, should be analyzed with caution. However, despite the aforementioned aspects, it is relevant to highlight the trends observed among the variables, which tend to be found in most of the studies that were chosen for this review, acquiring consistency, due to the number of publications that were analyzed.

In conclusion and based on what is stated in this manuscript, there is evidence that supports the idea that the presence of herpes virus in the periodontal tissues of systemically healthy adult patients with chronic periodontitis would influence its progression and severity.

It is essential to carry out randomized clinical trials to confirm a relationship between EBV, HSV, CMV, and periodontal disease.
CONCLUSION.

The results of this study suggest that the possible exacerbation of periodontal disease in the host could be associated with the co-infection of herpes virus-bacteria, in addition to factors specific to the host's immune system.

EBV, HCMV, and HSV viruses could be associated with the progression and severity of periodontal disease as they are related to a greater probing depth, greater clinical insertion loss, and greater bleeding on probing. A direct correlation between HSV and EBV viruses was found.

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REFERENCES.


