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Review

Association between chronic periodontitis and herpes viruses: A review of the literature.

Relación entre periodontitis crónica y virus herpes: Una revisión de la literatura.

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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 HCMV; 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, HCMV, 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.*

Resumen: Objetivo: Esta investigación tiene como objetivo analizar la literatura especializada disponible sobre la asociación entre Herpesvirus [*Citomegalovirus* (CMV), *virus de Epstein Barr* (EBV), *virus Herpes simplex* (HSV)] y periodontitis crónica para aclarar el posible papel de estos microorganismos en la progression y gravedad de la enfermedad. **Materiales y Métodos:** En marzo de 2019 se realizó una búsqueda de artículos científicos en los principales metabuscadores: PubMed/MEDLINE, SciELO, EBSCO y el motor de busqueda Trip, para seleccionar los artículos según los criterios de exclusión e inclusión. El análisis de los artículos se realizó a través de una matriz de datos expresada en tablas de frecuencia utilizando estadística descriptiva con medidas de

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tendencia central, dispersión y correlación. **Resultado:** Los resultados de este estudio muestran que la presencia de CMV, EBV y HSV en pacientes con periodontitis crónica está relacionada con un aumento de parámetros clínicos como la profundidad de la bolsa al sondaje (DP), la pérdida de inserción clínica (CIL) y el sangrado al sondaje. (BOP), en el 96%, 60% y 40% de los estudios, respectivamente, para HCMV; 96,55% (PD), 51,72% (CIL) y 48,28% (BOP) para EBV y 80% (PD), 90% (CIL) y 60% (BOP) para HSV. La prevalencia promedio de EBV, CMV y HSV fue del 46,3%, 35,4% y 40,1%, respectivamente. **Conclusion:** El EBV, el CMV y el HSV podrían estar asociados con la progresión y gravedad de la enfermedad periodontal, ya que se relacionan con una mayor profundidad de sondaje, mayor pérdida de inserción clínica y mayor sangrado al sondaje. El EBV presentó una mayor prevalencia en la literatura revisada. Se necesitan más estudios clínicos para verificar una relación directa entre EBV, HSV, CMV y enfermedad periodontal, para confirmar las tendencias observadas en este trabajo.

Palabra Clave: *Citomegalovirus; virus epstein-barr; virus herpes simplex; prevalencia; periodontitis; bolsa periodontal.*

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.

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.[6]

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.

Publication	Year	Study design	Sample size	Type of samples technique	Sample extraction	PCR type	EBV	HSV	CMV
Hernández *et al.,*[2]	2016	Case-control study	11	Gingival crevicular fluid	Paper points	Nested	17	27	*
Wu *et al.,*[7]	2007	Case-control study	143	Subgingival biofilm	Paper points	Nested	63.6	*	79
Shah *et al.,*[11]	2016	Case-control study	40	Gingival crevicular fluid	Paper points	Multiple	25	37	*
Kazi *et al.,*[12]	2015	Cross-sectional study	75	Subgingival biofilm	Curettes	Multiple	37.33	28	30.66
Kato *et al.,*[17]	2013	Case-control study	85	Subgingival biofilm	Paper points	Nested	66	*	*
Das *et al.,*[18]	2012	Case-control study	10	Subgingival biofilm	Curettes	Multiple	32	76	28
Botero *et al.,*[20]	2007	Case-control study	20	Subgingival biofilm	Paper points	Nested	*	*	60
Imbronito *et al.,*[21]	2008	Case-control study	40	Subgingival biofilm	Paper points	Nested	46.7	40	50
Bilder *et al.,*[22]	2013	Case-control study	59	Stimulated saliva	Plastic tubes	Real-time	40	5	15
Saygun *et al.,*[26]	2002	Case-control study	30	Subgingival biofilm	Paper points	Nested	16.7	6.7	44.3
Li Ying *et al.,*[27]	2004	Case-control study	62	Subgingival biofilm	Paper points	Nested	58	*	*
Ling *et al.,*[28]	2004	Cross-sectional study	20	Subgingival biofilm	Paper points	Nested	15	50	75
Tantivanich *et al.,*[29]	2004	Case-control study	50	Gingival crevicular fluid	Paper points	Nested	*	*	8
Idesawa *et al.,*[30]	2004	Cross-sectional study	33	Stimulated saliva	Plastic tubes	Real-time	48.5	*	*
Klemen *et al.,*[31]	2005	Cross-sectional study	66	Gingival crevicular fluid	Paper points	Nested	44	*	3
Konstantinidis *et al.,*[32]	2005	Case-control study	22	Gingival crevice	Paper points	Real-time	55	*	*
Wu *et al.,*[33]	2006	Case-control study	65	Subgingival biofilm	Paper points	Nested	66	*	*
Moghim *et al.,*[34]	2007	Cross-sectional study	61	Subgingival biofilm	Curettes	Nested	60.7	*	*
Saygun *et al.,*[35]	2008	Case-control study	15	Subgingival biofilm	Curettes	Real-time	60	*	53
Rotola *et al.,*[37]	2008	Case-control study	24	Gingival tissue	Biopsy	Nested	50	*	*
Combs *et al.,*[38]	2008	Case-control study	13	Subgingival biofilm / Saliva	Curettes	Real-time	*	*	8.8
Chalabi *et al.,*[39]	2008	Case-control study	80	Subgingival biofilm	Curettes	Nested	72.5	*	50
Nishiyama *et al.,*[40]	2008	Case-control study	50	Subgingival biofilm	Paper points	Nested	*	46.4	*
Botero *et al.,*[41]	2008	Case-control study	37	Gingival crevicular fluid	Paper points	Nested	*	*	80
Chalabi *et al.,*[42]	2010	Case-control study	40	Subgingival biofilm	Curettes	Nested	72.5	*	50
Grenier *et al.,*[46]	2009	Case-control study	31	Gingival crevicular fluid	Paper points	Nested	3	13	35
Dawson *et al.,*[43]	2009	Cross-sectional study	65	Saliva Plastic tubes	Real-time	82	*	2	
Bilichodmat *et al.,*[44]	2009	Case-control study	19	Subgingival biofilm	Curettes	Multiple	78	100	26
Sharma *et al.,*[47]	2012	Case-control study	20	Subgingival biofilm	Curettes	Nested	25	*	20
Tomasini *et al.,*[48]	2012	Case-control study	20	Periodontal pocket	Biopsy	Nested	*	*	30
Vincent-Bugnas *et al.,*[49]	2013	Cross-sectional study	20	Subgingival biofilm	Curettes	Real-time	13	*	*
Petrovic *et al.,*[50]	2014	Case-control study	36	Gingival crevicular fluid	Paper points	Nested	*	38.9	*
Kato *et al.,*[51]	2015	Case-control study	25	Subgingival biofilm	Paper points	Real-time	68	*	*
Khosropanaha *et al.,*[52]	2015	Case-control study	75	Saliva/Gingival tissue	Paper points	Real-time	51.3	*	21.6
Kazi *et al.,*[53]	2017	Case-control study	300	Subgingival biofilm	Curettes	Multiple	30.6	46.6	19.3

***:** Not available. **EBV:** Epstein-Barr Virus. **HSV:** Herpes Simplex virus type 1. **CMV:** Cytomegalovirus.

Table 2. Statistical analysis of the sample.

Sample size	Patients
Lowest	10
1st Qu	21.5
Median	34.5
Mean (Average)	42.8
3rd Qu	62.7
Highest	300
Standard Deviation (SD)	26.8

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

Total number of studies		39	
Number of studies that analyzed the virus		**25**	
		Frequency	**CMV %**
Periodontopathogens	Treponema denticola	0	0
	Porphyromonas gingivalis	7	28
	Tannerella forsythia	4	16
	Aggregatibacter actinomycetemcomitans	0	0
	Fusobacterium nucleatum	0	0
	Porphyromona 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.

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

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.[59]

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%), Tanerella 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 Tanerella 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.

Total number of studies		**39**	
Number of studies that analyzed the virus		**29**	
		Frequency	**CMV %**
Periodontopathogens	Treponema denticola	1	3.45
	Porphyromonas gingivalis	7	24.14
	Tannerella forsythia	4	13.79
	Aggregatibacter actinomycetemcomitans	1	3.45
	Fusobacterium nucleatum	2	6.9
	Porphyromona nigrescens	1	3.45
	Prevotella intermedia	2	6.9
Cells	B lymphocytes	15	51.72
	T lymphocytes	4	13.79
	Macrophages	3	10.34
	PMN	4	13.79
	Osteoclasts	1	3.45
Enzymes	Metalloproteinases	0	0
Proinflammatory cytokines	IL-1	3	10.34
	IL-6	2	6.9
	IL-10	1	3.45
	IL-4	1	3.45
	TNF-α	3	10.34
Clinical parameters	Probing depth	28	96.55
	Clinical insertion loss	15	51.72
	Gingival bleeding	14	48.28

Table 6. Spearman's correlation coefficient between EBV, HSV, and CMV.

COR(X)	EBV	HSV	CMV
EBV	1.00	0.70	-0.27
HSV	0.70	1.00	-0.05
CMV	-0.27	-0.05	1.00

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.[8] Because of this, the participation of other microorganisms has been suggested, specifically herpes virus, in the etiology and pathogenesis of the disease.[9-10]

In this regard, Shah *et al.*,[11] detected the presence of this virus in 96.7% of patients diagnosed with chronic 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.[18,19]

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.[11,16]

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 cells (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.[18]

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.

1. Pinto G, Silva MD, Peddey M, Sillankorva S, Azeredo J. The role of bacteriophages in periodontal health and disease. Future Microbiol. 2016;11:1359-1369.
2. Hernández HH. Herpes Simplex Virus 1, Cytomegalovirus and Epstein Barr Virus Detection in Patients with Chronic and Aggressive Periodontitis. Open Access Library Journal. 2016;3(03):1.
3. Papone V, Verolo C, Zaffaroni L, Batlle A, Capó C, Bueno L, Gamonal J, Silva, N, Soria S. Detección y prevalencia de patógenos periodontales de una población con periodontitis crónica en Uruguay mediante metodología convencional y metagenómica. ODONTOESTOMATOLOGÍA. 2015; XVII(25): 23-32.
4. Ishikawa I. Host responses in periodontal diseases: a preview. Periodontol 2000. 2007; 43:9-13.
5. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
6. Hernández R, Fernández C, Baptista P. Metodología de la investigación. México: McGraw-Hill, 2010.
7. Wu YM, Yan J, Ojcius DM, Chen LL, Gu ZY, Pan JP. Correlation between infections with different genotypes of human cytomegalovirus and Epstein-Barr virus in subgingival samples and periodontal status of patients. J Clin Microbiol. 2007;45(11):3665-70.
8. Zhu C, Li F, Wong MC, Feng XP, Lu HX, Xu W. Association between Herpesviruses and Chronic Periodontitis: A Meta-Analysis Based on Case-Control Studies. PLoS One. 2015;10(12):e0144319.
9. Contreras A, Botero JE, Slots J. Biology and pathogenesis of cytomegalovirus in periodontal disease. Periodontol. 2000;64(1):40-56.
10. Binshabaib M, ALHarthi SS, Salehpoor D, Michelogiannakis D, Javed F. Contribution of herpesviruses in the progression of periodontal and peri-implant diseases in systemically healthy individuals. Rev Med Virol. 2018; 28:e1996.
11. Shah R, Mehta DS. Prevalence of herpesviruses in gingivitis and chronic periodontitis: relationship to clinical parameters and effect of treatment. J Indian Soc Periodontol. 2016;20(3):279-85.
12. Kazi MM, Bharadwaj R, Bhat K, Happy D. Association of Herpes Viruses with Mild, Moderate and Severe Chronic Periodontitis. J Clin Diagn Res. 2015;9(7):DC05-8.
13. Mombelli A. Microbial colonization of the periodontal pocket and its significance for periodontal therapy. Periodontology 2000. 2018; 76(1), 85-96.
14. Srivastava AK, Shukla S, Srivastava P, Dhole TN, Nayak MT, Nayak A, Mathur A. Real time detection and quantification of Epstein Barr virus in different grades of oral gingivitis and periodontitis patients. J Exp Ther Oncol. 2019;13(1):9-14.
15. Slots J. Periodontal herpesviruses: prevalence, pathogenicity, systemic risk. Periodontology 2000. 2015;69(1), 28-45.
16. Contreras A, Botero JE, Slots J. Biology and pathogenesis of cytomegalovirus in periodontal disease. Periodontol 2000. 2014;64(1):40-56.
17. Kato A, Imai K, Ochiai K, Ogata Y. Higher prevalence of Epstein-Barr virus DNA in deeper periodontal pockets of chronic periodontitis in Japanese patients. PLoS One. 2013;8(8):e71990.
18. Das S, Krithiga GS, Gopalakrishnan S. Detection of human herpes viruses in patients with chronic and aggressive periodontitis and relationship between viruses and clinical parameters. J Oral Maxillofac Pathol.2012;16(2):203-9.
19. Contreras A, Botero, JE, Slots J. Biology and pathogenesis of cytomegalovirus in periodontal disease. Periodontology 2000. 2014; 64(1), 40-56.
20. Botero J E, Parra B, Jaramillo A, Contreras A. Subgingival human cytomegalovirus correlates with increased clinical periodontal parameters and bacterial coinfection in periodontitis. Journal of periodontology, 2007; 78(12), 2303-10.
21. Imbronito AV, Okuda OS, Maria de Freitas N, Moreira Lotufo RF, Nunes FD. Detection of herpesviruses and periodontal pathogens in subgingival plaque of patients with chronic periodontitis, generalized aggressive periodontitis, or gingivitis. J Periodontol. 2008;79(12):2313-21.
22. Bilder L, Elimelech R, Szwarcwort-Cohen M, Kra-Oz Z, Machtei EE. The prevalence of human herpes viruses in the saliva of chronic periodontitis patients compared to oral health providers and healthy controls. Arch Virol. 2013; 158:1221–6.
23. Imai K, Ogata Y. How Does Epstein-Barr Virus Contribute to Chronic Periodontitis? Int J Mol Sci. 2020;21(6):1940.
24. Bertoldi C, Pellacani C, Lalla M, Consolo U, Pinti M, Cortellini P, Cossarizza A. Herpes Simplex I virus impairs regenerative outcomes of periodontal regenerative therapy in intrabony defects. A pilot study. Journal of clinical periodontology. 2012; 39(4), 385-92.
25. Ivanovska-Stojanoska M, Popovska M, Anastasovska V, Kocova M, Zendeli-Bedzeti L, Dimova C, Taseva A. Detection of Virus Herpes Simplex Type 1 in Patients with Chronic Periodontal Disease. Open Access Maced J Med Sci. 2018;6(9):1737-41.
26. Saygun I, Sahin S, Ozdemir A, Kurtiş B, Yapar M, Kubar A, Ozcan G. Detection of human viruses in patients with chronic periodontitis and the relationship between viruses and clinical parameters. J Periodontol. 2002;73(12):1437-43.
27. Li Y, Zhang JC, Zhang YH. [The association between infection of Epstein-Barr virus and chronic periodontitis]. Zhonghua Kou Qiang Yi Xue Za Zhi. 2004;39(2):146-8.
28. Ling LJ, Ho CC, Wu CY, Chen YT, Hung SL. Association between human herpesviruses and the severity of periodontitis. J Periodontol. 2004;75(11):1479-85.
29. Tantivanich S, Laohapand P, Thaweeboon S, Desakorn V, Wuthinuntiwong P, Chalermtaranukul S, Pansri P, Amarapal P, Balachandra K, Chantratita W, Dhepakson P. Prevalence of cytomegalovirus, human herpesvirus-6, and Epstein-Barr virus in periodontitis patients and healthy subjects in the Thai population. Southeast Asian J Trop Med Public Health. 2004;35(3):635-40.
30. Idesawa M, Sugano N, Ikeda K, Oshikawa M, Takane M, Seki K, Ito K. Detection of Epstein-Barr virus in saliva by real-time PCR. Oral Microbiol Immunol. 2004;19(4):230-2.
31. Klemenc P, Skalerič U, Artnik B, Nograšek P, Marin J. Prevalence of some herpesviruses in gingival crevicular fluid. Journal of clinical virology. 2005; 34(2), 147-152.
32. Konstantinidis A, Sakellari D, Papa A. and Antoniadis, A. Real-time polymerase chain reaction quantification of Epstein–Barr virus in chronic periodontitis patients. J Periodon Res. 2005; 40: 294-8.

33. Wu YM, Yan J, Chen LL, Sun WL, Gu ZY. Infection frequency of Epstein-Barr virus in subgingival samples from patients with different periodontal status and its correlation with clinical parameters. J Zhejiang Univ Sci B. 2006;7(11):876-83.

34. Moghim SH, Chalabi M, Abed AM, Rezaei F, Tamizifar H. Prevalence of Epstein-Barr virus type 1 in patients with chronic periodontitis by nested-PCR. Pak J Biol Sci. 2007;10(24):4547-50.

35. Saygun I, Kubar A, Şahin S, Şener K, Slots J. Quantitative analysis of association between herpesviruses and bacterial pathogens in periodontitis. J Periodontal Res. 2008; 43(3):352–359

36. Botero JE, Vidal C, Contreras A, Parra B. Comparison of nested polymerase chain reaction (PCR), real-time PCR and viral culture for the detection of cytomegalovirus in subgingival samples. Oral Microbiol Immunol.2008;3(3), 239-44.

37. Rotola A, Cassai E, Farina R, Caselli E, Gentili V, Lazzarotto T, Trombelli L. Human herpesvirus 7, Epstein-Barr virus and human cytomegalovirus in periodontal tissues of periodontally diseased and healthy subjects. J Clin Periodontol. 2008;35(10):831-7.

38. Combs DR, Reilly EA, Dawson III DR, Avdiushko SA, Danaher RJ, & Miller CS. Detection of human cytomegalovirus in dental plaque from individual periodontal sites by real-time polymerase chain reaction. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology. 2008; 106(6), 840-44.

39. Chalabi M, Moghim S, Mogharehabed A, Najafi F, Rezaie F. EBV and CMV in chronic periodontitis: a prevalence study. Arch Virol. 2008;153(10):1917-9.

40. Nishiyama SA, Nakano V, Velásquez-Melendez G, Avila-Campos MJ. Occurrence of herpes simplex virus 1 and three periodontal bacteria in patients with chronic periodontitis and necrotic pulp. Can J Microbiol. 2008;54(4):326-30.

41. Grenier G, Gagnon G, Grenier D. Detection of herpetic viruses in gingival crevicular fluid of patients suffering from periodontal diseases: prevalence and effect of treatment. Oral Microbiol Immunol. 2009;24(6):506-9.

42. Chalabi M, Rezaie F, Moghim S, Mogharehabed A, Rezaei M, Mehraban B. Periodontopathic bacteria and herpesviruses in chronic periodontitis. Mol Oral Microbiol. 2010;25(3):236-40.

43. Dawson DR 3rd, Wang C, Danaher RJ, Lin Y, Kryscio RJ, Jacob RJ, Miller CS. Salivary levels of Epstein-Barr virus DNA correlate with subgingival levels, not severity of periodontitis. Oral Dis. 2009;15(8):554-9.

44. Bilichodmath S, Mangalekar SB, Sharma DC, Prabhakar AK, Reddy SB, Kalburgi NB, Patil SR, Bhat K. Herpesviruses in chronic and aggressive periodontitis patients in an Indian population. J Oral Sci. 2009;51(1):79-86.

45. Saygun I, Kubar A, Ozdemir A, Slots J. Periodontitis lesions are a source of salivary cytomegalovirus and Epstein-Barr virus. J Periodontal Res. 2005;40(2):187-91.

46. Monzón J, Acuña M, Canga E, Ortega S. Prevalencia de herpes virus en bolsas periodontales de pacientes asistidos en la Cátedra de Periodoncia de la FOUNNE / Prevalence of herpes virus in periodontal pockets of patients assisted at the Periodontics Department, FOUNNE. Rev. Fundac Juan Jose Carraro.2011;16(34):36-49.

47. Sharma R, Padmalatha O, Kaarthikeyan G, Jayakumar ND, Varghese S, Sherif K. Comparative analysis of presence of Cytomegalovirus (CMV) and Epsteinbarr virus -1 (EBV-1) in cases of chronic periodontitis and aggressive periodontitis with controls. Indian J Dent Res. 2012;23(4):454-8.

48. Thomasini RL, Bonon SH, Durante P, Costa SC. Correlation of cytomegalovirus and human herpesvirus 7 with CD3+ and CD3+ CD4+ cells in chronic periodontitis patients. J Periodontal Res. 2012;47(1):114-120.

49. Vincent-Bugnas S, Vitale S, Mouline CC, Khaali W, Charbit Y, Mahler P, Prêcheur I, Hofman P, Maryanski JL, Doglio A. EBV infection is common in gingival epithelial cells of the periodontium and worsens during chronic periodontitis. PLoS One. 2013;8(12):e80336.

50. Petrović SM, Zelić K, Milasin J, Popović B, Pucar A, Zelić O. Detection of herpes simplex virus type 1 in gingival crevicular fluid of gingival sulcus/periodontal pocket using polymerase chain reaction. Srp Arh Celok Lek. 2014;142(5-6):296-300.

51. Kato A, Imai K, Ochiai K, Ogata Y. Prevalence and quantitative analysis of Epstein-Barr virus DNA and Porphyromonas gingivalis associated with Japanese chronic periodontitis patients. Clin Oral Investig. 2015;19(7):1605-10.

52. Khosropanah H, Karandish M, Ziaeyan M, Jamalidoust M. Quantification of Epstein-Barr Virus and Human Cytomegalovirus in Chronic Periodontal Patients. Jundishapur J Microbiol. 2015;8(6):e18691.

53. Kazi MMAG, Bharadwaj R. Role of herpesviruses in chronic periodontitis and their association with clinical parameters and in increasing severity of the disease. Eur J Dent. 2017;11(3):299-304.