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ORIGINAL ARTICLE

Viruses in pulp and periapical inflammation: a review

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Abstract The presence of viruses in endodontic disease has been studied in the last decade. Their presence is associated with periapical radiolucency and with clinical findings, such as pain. The aim of this review is to analyze the scientific evidence currently published about viruses in pulp and periapical inflammation, and its possible clinical implications. A literature review was carried out using the Medline/Pubmed database. The search was performed, in English and Spanish, using the following keyword combinations: virus AND endodontic; virus AND periapical; virus AND pulpitis; herpesvirus AND periapical; papillomavirus AND periapical. We subsequently selected the most relevant studies, which complied with the search criterion. A total of 21 articles were included, of which 18 detected the present of viruses in the samples. In 3 of the studies, viral presence was not found in the samples studied. The Epstein–Barr virus was found in about 41 % of cases compared to controls, in which it was present in about 2 %. The main association between viruses and endodontic pathosis is between Cytomegalovirus and Epstein–Barr virus; these are found in 114 of the 406 samples of different endodontic pathosis. Some evidence supports that the Epstein–Barr virus is present in a significant number of endodontic diseases, without exact knowledge of their action in these diseases.

Keywords Apical periodontitis · Epstein–Barr virus · Herpesvirus · Papillomavirus · Human cytomegalovirus

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Introduction

Bacterial infection of the root canal system may provoke apical periodontitis (AP), an acute or chronic inflammatory process in the periradicular tissues [1]. The clinical characteristics of the inflammatory response of the periapical tissues depend upon the different microbiological profiles and the immune response of the host [2, 3]. AP is a remarkably prevalent problem [4, 5]. The importance of AP is not only due to its impact on the oral cavity, but also to its possible association with different systemic diseases, conditions or habits such as diabetes mellitus [6, 7], smoking [8, 9], coronary heart disease [10–13], hypertension [14] and others [15, 16].

When the virus infects, the host reacts to the infecting virus through innate and adaptive immune responses, and the viral disease could be a direct result of cell destruction

or a consequence of host immune reactions against viral proteins. In turn, the host usually performs a delicate balancing act between promoting antiviral cytokine responses and limiting the amount of tissue damage [17].

Many viruses are ulcer-causing and carcinogenic agents in the oral region. They are also common infections in the oral mucosa and the perioral region. The oral conditions most commonly related to viral agents are oral ulcers, tumors and other pathologies such as periodontal disease, lichen planus, or Sjögren syndrome [17–23]. In the last 15 years, there has been growing interest in studying the presence of different viruses in periapical lesions. Different detection techniques have been used, particularly the use of immunohistochemistry and detection by polymerase chain reactions (PCR) [24–26]. Most of these studies have analyzed the association between the presence of viruses in apical periodontitis and their correlation with clinical characteristics, such as painful symptoms and bone damage. The investigations of these etiological agents have focused on the detection of viruses from the family *herpesviridae*. In particular, the studies have centered their attention on the Epstein–Barr virus (EBV), Cytomegalovirus (HCMV) and Herpes simplex (HSV-1 and HSV-2). However, in recent studies researchers have also detected the presence of other viruses pertaining to the family *herpesviridae* such as HHV-6 and HHV-8, as well as searching for and detecting the presence of Human Papillomavirus (HPV) [27, 28].

Herpesvirus and viruses pertaining to the family *herpesviridae* are the largest viral family present in the oral cavity. *Herpesviridae* correspond to a DNA virus (linear double helix), with a virion size ranging 120–150 nm. *Herpesviridae* present an icosahedral capsid, proteinaceous integument, and a sheath with viral glycoproteins. There are 8 known types of human *herpesviridae*: Herpes simplex 1 (HSV-1), Herpes simplex 2 (HSV-2), Varicella-zoster (VZV) or herpes virus 3, Epstein–Barr (EBV) or herpes virus 4, Cytomegalovirus (HCMV) or herpes virus 5, Herpes virus 6 (HHV-6), 7 (HHV-7) and 8 (HHV-8). Each of these viruses differs in their clinical and biological characteristics [17]. It is hypothesized that these viruses, when they are present in the apical lesions or pulp tissue, could cause exacerbated symptoms in patients or the presence of large radiolucent lesions. Moreover, in patients with some degree of immunosuppression, the presence of these viruses may have implications that prevent or delay proper healing of tissues.

The aim of this review is to analyze the scientific evidence currently published about the presence of viruses in pulp and periapical inflammation, and its possible clinical implications.

Materials and methods

A review according to the PRISMA 2009 checklist was performed. The MEDLINE search (PubMed) of articles published prior to April 7, 2014 was conducted using the following keywords and Boolean operators: virus AND endodontic; virus AND periapical; virus AND pulpitis; herpesvirus AND periapical; papillomavirus AND periapical. Any relevant work published, in both English and Spanish, and containing information about the described issue, was considered for inclusion in the review. The articles were initially evaluated by title and abstract, and later according to their relationship with the topics, and the full text was then reviewed. Additional manual searches were performed to examine the bibliographies of the retrieved publications and of other previous reviews. Inclusion criteria were: (1) Controlled and/or random clinical studies, observational prevalence studies, case–control studies. (2) Studies that determined the presence of viruses in pulp or periapical tissue, or acute abscesses of endodontic origin, in direct or indirect form. (3) Studies that specified the number of patients and/or samples, the intervention carried out, and the method used to determine the presence of the virus. (4) Studies that clearly indicated the virus or the viruses being the studies. To conduct a validity assessment, one reviewer (J. L-L) screened the abstracts of the search results for compliance with the inclusion criteria. After the abstracts were read, the full texts of studies with questionable potential for inclusion were further analyzed. A second reviewer (S. H-V) reconsidered studies included as well as exclusions. Disagreements were clarified by discussion between the two reviewers. Exclusion criteria were: (1) Of multiple studies which used their samples from another published study, only one study was considered. (2) Studies that lacked specification of important aspects of the methodology.

When doubt existed about the inclusion of patients considered in similar articles, authors were contacted via email. These contacts were specifically done for the works of Slots et al. [2], Li et al. [25], Sabeti et al. [29], Sabeti and Slots [30] and Chen et al. [31]. The articles were revised and checked with the list of points from the STROBE declaration [32]. Finally, the studies that comply the majority review points, according to the type of observational study, were included. The selection process is shown in Fig. 1.

Data were introduced in an Excel spreadsheet containing: author name and country, year of publication, type of study, main objective, viruses studied, participants (number, clinical characteristics such as symptoms and radiographic characteristics in the pertinent cases), sample

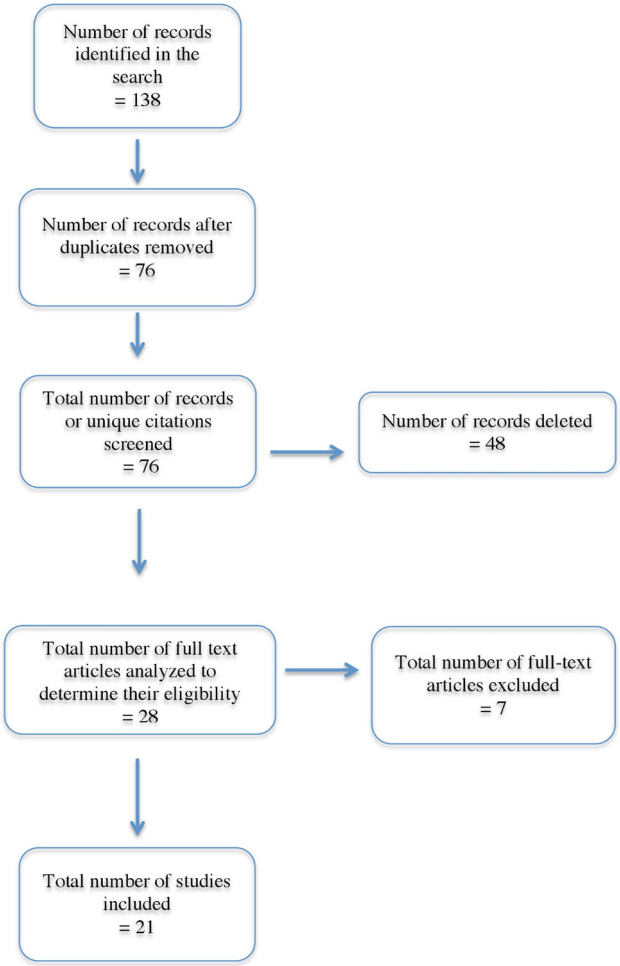

Fig. 1 Flowchart of paper selection process

(number, type and means of collection), control group, loss of participants, analyses carried out on the sample, and results.

Results

The results of the search are shown in Table 1. The review included 21 studies in which the presence of different viruses in pulp and periapical inflamed tissues, and apical abscess purulent exudates, were evaluated, particularly from the family *herpesviridae*.

HSV-1 and HSV-2 were studied in 10 investigations, with negative results in 5 of them. In the other studies, they appeared only in a few samples, 16 samples were positive from a total of 283 and two positive controls with a total of 37. VZV was analyzed in 146 samples, having positive results in three samples.

EBV was searched for in a total of 520 samples (17 studies) and was present in 213 samples (41 %) and in two

Table 1 Results of searching the database

Search words	No. studies
virus AND endodontic	35
virus AND periapical	56
virus AND pulpitis	11
herpesvirus AND periapical	33
papillomavirus AND periapical	3

control tissues (about 2 %) from a total of 81. HCMV was searched for in 18 of the 21 studies, in a total of 553 cases of endodontic diseases, appearing in 187 cases. In controls ($n = 81$), it was present in nine.

Three of the studies were negative for the viruses in all of the samples, which correspond to irreversible pulpitis, apical periodontitis (symptomatic and asymptomatic), and acute apical abscesses. HHV-6 (types A and B) was searched for in 73 cases of endodontic diseases, within which were purulent exudate of apical abscess and apical periodontitis tissues, appearing positive in 10 cases. In controls ($n = 40$) they appear only in one. HHV-7 was present in only one sample in a total of 33 cases of endodontic diseases and in controls ($n = 5$); they were also is present in one sample. HHV-8 was searched in a total of 33 cases, appearing positive in 18 cases, and in two controls ($n = 5$). HPV has been searched in a total of 55 cases of endodontic diseases and was present in 3 cases. In controls ($n = 5$), it did not appear in any samples. The results for each virus are present in Table 2.

The main association between viruses was between HCMV and EBV, which were found in 114 of the 406 samples of different endodontic diseases. All of the studies correspond to observational studies. The characteristics for each study are presented in Table 3.

Discussion

Association between viruses and pulpitis or apical periodontitis

HSV-1 and 2, VZV, HHV-7 and HPV were detected in a very low number of cases in endodontic pathosis. VZV was present in a low number of samples ($n = 3$); one of them corresponded to a case of symptomatic irreversible pulpitis. The authors concluded that it could have been a wrong diagnosis of herpes zoster, whose symptomatology was confused with pulpal inflammation [25]. It is important to do differential diagnosis in these cases, to avoid making misdiagnoses resulting in unnecessary dental treatment. EBV was the virus most associated with endodontic

Table 2 Summary of cases with endodontics pathosis and healthy control tissues affected by a virus

Virus	No. positive/No. endodontic pathosis	No. positive/No. healthy control tissues	Virus in endodontic pathosis (%)	Virus in healthy control tissues (%)
HSV 1 and 2	16/281	1/37	5.69	6.25
VZV	3/146	0/19	2.05	0
EBV	213/520	2/81	40.96	2.47
HCMV	187/553	9/81	33.81	11.11
HHV 6A and B	10/73	1/40	13.70	2.5
HHV-7	1/33	1/5	3.03	20
HHV-8	18/33	2/5	54.55	40
HPV	3/55	0/5	5.45	0

diseases. Seventeen studies have investigated the presence of EBV in pulpitis, acute apical abscesses or apical periodontitis [2, 25, 26, 28–31, 34–43]. In all these studies, the EBV was present in the samples, with the exception of Rosaline's study [35]. In this study the low number of samples, probably explains this event; and also, the tissues of the samples corresponded to inflamed pulp tissue (irreversible pulpitis), while in other studies, apical tissues from teeth with apical periodontitis were used.

This virus is related to a greater percentage of endodontic diseases; but it still remains to determine the role that EBV could play on endodontic diseases. For example, it may be a primary or secondary factor in the establishment of symptoms such as pain or larger apical lesions, or it may correspond to a minor, or no, clinical relevance event.

About HCMV found in the samples with endodontic diseases, these samples did not show differences statistically significant with the control groups [25, 37]. Adric et al. [43] studied the presence of HCMV in radicular cysts and keratocysts, finding the virus present in both types of odontogenic cysts, without significant differences.

Note that the number of cases and control used for the study of this virus as well as the other are very dissimilar (Table 3). Even many studies do not use healthy controls, so that it would be desirable in future studies, to include equal numbers and the same tissue of cases and healthy controls tissue to enable more accurate comparisons.

The main association between viruses and endodontic diseases, that was HCMV and EBV, but still remains to be determined whether these associations have an effect on the symptoms or radiographic characteristics of apical lesions, or only have a minor clinical finding [2, 25, 26, 29, 30, 34, 36, 37, 39–43].

In the pediatric population, the study by Yildirim et al. [41] is the only one that evaluates the presence of EBV and HCMV in deciduous teeth with symptomatic periapical pathosis, finding that EBV and HCMV are statistically different in comparison with a control group. However, the sample is small and the control group is not apical tissue, but rather, healthy tissue pulp of permanent teeth was used, so it would be interesting to know whether these results vary when they are compared to a greater number of cases and a similar control tissue. Another study that is important to note is one by Saboia-Dantas et al. [40], in which the presence of EBV and HCMV was evaluated with immunohistochemistry in patients HIV+ and HIV− with asymptomatic apical lesions. The EBV was not statistically different between the patients HIV+ and HIV−. In contrast the HCMV shows a significant difference between the patients HIV+ and HIV−. These results are not surprising in patients HIV+; since in these patients, HCMV occurs most frequently.

About the detection of HHV-6, new studies are needed on this virus since the results are limited only to these two investigations [28, 44], and only one also had healthy tissues control.

The presence of HHV-7 and HHV-8 has been recently reported in acute apical abscesses [28]. HHV-7 apparently has no importance in the development of endodontic disease. Surprisingly, this study has reported a high prevalence of HHV-8 in acute apical abscesses, with a finding of ~55 %. This virus is strongly associated with the HIV+ population; however, any of the patients studied were HIV+ [28].

HPV, of the Papillomaviridae family, is a double-helix circular virus with more than 150 types. It is a small virus without a sheath, with tropism toward the epithelial tissues. In humans it is associated with a variety of proliferative epithelial lesions; some types are even associated with premalignant or malignant conditions [46–49]. However, few studies have described its presence in association with endodontic diseases. Two studies [24, 28] had results that did not differ with the prevalence of oral HPV (0.9–7.5 %) [49], so it possibly does not have a predominant role. Further studies with other cases of endodontic diseases are needed and adding similar control groups.

Table 3 Characterization of the observational studies included in the review

Author/year/country/reference	Sample number/material type	Controls number/types	Virus	Analytical procedure	Results Virus (+) or (−)
Rider et al. 1995, USA [24]	20/Radicular cysts	No	HSV-1	Immunohistochemistry	HSV-1 (−)
			HSV-2		HSV-2 (−)
			HPV		HPV (−)
Heling et al. 2001, Israel [33]	38/Pulp and periapical tissue	8/Healthy pulp tissue	HSV	PCR	HSV (−)
Sabeti et al. 2003, USA [29]	14/Periapical tissue	No	HSV	PCR (reverse transcription)	HSV (+)
			EBV		HCMV (+)
			HCMV		EBV (+)
Sabeti al. 2003, USA [26]	5/Periapical tissue	No	HSV	PCR (reverse transcription)	HSV (−)
			EBV		EBV (+)
			HCMV		HCMV (+)
Sabeti et al. 2003, USA [34]	14/Periapical tissue	2/Healthy periapical tissue	HSV	PCR (reverse transcription)	HSV (−)
			EBV		EBV (+)
			HCMV		HCMV (+)
Slots et al. 2004, USA [2]	44/Periapical tissue	No	EBV	PCR (reverse transcription)	EBV (+)
			HCMV		HCMV (+)
Sabeti et al. 2004, USA [30]	34/Periapical tissue	No	HSV	PCR (reverse transcription)	HSV (+)
			EBV		EBV (+)
			HCMV		HCMV (+)
Yildirim et al. 2006, Turkey [41]	12/Deciduous teeth periapical tissue	12/Healthy pulp tissue permanent teeth	EBV	PCR (reverse transcription)	EBV (+)
			HCMV		HCMV (+)
Saboia-Dantas et al. 2007, Brazil [40]	35/Periapical tissue (26 VIH−/9 VIH+)	No	EBV	Immunohistochemistry	EBV (+)
			HCMV		HCMV (+)
Andric et al. 2007, Serbia [44]	43/Odontogenic cysts	No	HCMV	PCR	HCMV (+)
Yazdi et al. 2008, Iran [39]	50/Periapical tissue	No	EBV	PCR (reverse transcription)	EBV (+)
			HCMV		HCMV (+)
Sunde et al. 2008, Norway [38]	40/Periapical tissue	No	EBV	PCR (real time)	EBV (+)
			HCMV	In situ hybridization	HCMV (−)
				Immunohistochemistry	
Rosaline et al. 2009, India [35]	10/Pulp tissue	8/Healthy pulp tissue	HSV	PCR	HSV (−)
			EBV		EBV (−)
			HCMV		HCMV (−)
Chen et al. 2009, USA [31]	31/Purulent exudate acute apical abscess and cellulitis	19 (from reference 25)/ Healthy pulp tissue	HSV-1	PCR	HSV (+)
			VZV	PCR nested	VZV (−)
			EBV (type 1 and 2)		EBV (+)
					HCMV (+)
			HCMV		
Li et al. 2009, USA [25]	82/Pulp and periapical tissue	19/Healthy pulp tissue	HSV-1	PCR	HSV-1 (+)
			VZV	PCR nested	VZV (+)
			EBV (Type 1 and 2)	PCR (reverse transcription)	EBV (+)
					HCMV (+)
			HCMV		
Hernádi et al. 2010, Hungary [37][a]	40/Periapical tissue	40/Healthy pulp tissue	EBV	PCR (reverse transcription)	EBV (+)
			HCMV		HCMV (+)
Hernádi et al., 2011, Hungary [45][a]	40/Periapical tissue	40/Healthy pulp tissue	HHV-6A	PCR nested	HHV-6A (+)
			HHV-6B		HHV-6B (+)

Table 3 continued

Author/year/country/reference	Sample number/material type	Controls number/types	Virus	Analytical procedure	Results Virus (+) or (−)
Ferreira et al. 2011, Brazil [28][b]	33/Acute apical abscess purulent exudate	No	HPV Herpes viruses (1–8)	PCR nested	HHV-8 (+) HHV-7 (+) HHV-6 (+) EBV (+) HPV (+) HSV-1/2 (+) VZV (+) HCMV (−)
Sabeti et al. 2012, USA [36]	15/Periapical tissue	No	EBV HCMV	PCR (reverse transcription)	EBV (+) HCMV (+)
Ozbek et al. 2012, Turkey [42]	28/Periapical tissue	No	EBV HCMV	PCR (real time)	EBV (+) HCMV (+)
Verdugo et al. 2013, USA [43]	33/Periapical tissue	No	EBV HCMV	PCR (real time)	EBV (+) HCMV (+)

PCR polymerase chain reaction, (+) virus presence, (−) virus absence

[a] They use the same participants and samples, but detected other viruses

[b] Consider another study samples, but adds 10 new samples [27, 28]

Virus and clinical findings

Some studies tried to correlate the presence of a virus or viruses with endodontic diseases that show tumefaction, pain, and sensitivity to chewing, palpation or percussion.

EBV and HCMV, when present, alone or together, are associated frequently with symptomatic lesions [2, 29, 30, 36]. However, in other studies, no relationship has been found between the viral presence and symptoms in endodontic diseases [26, 37, 42, 44].

In relation to the presence of viruses and the size of the periapical lesion, one problem is the definition of the size of the lesions used by each author. Some authors considered that lesions over 5 mm were "large periapical lesions", and any smaller are considered "small periapical lesions" [25, 37, 45]. However, in other studies, this difference was not specified [26, 30, 34]. Sabeti et al. [34], Sabeti and Slots [30], as well as Hernádi et al. [37, 45] found a relationship between the presence of the viruses EBV, HCMV and HHV-6 subtype B in large apical lesions. On the contrary, Li et al. [25] did not find a statistically significant difference.

The pathway to the pulp or apical tissue

The spread of the virus to the apical or pulp tissue can be achieved through saliva contamination in the case of teeth with coronary destruction, producing a communication between the pulp chamber and root canals with the saliva. In teeth with sinus tract, it can also be presumed that the pathway contamination is from the saliva to the apical lesion. Another pathway is in endodontic access, since the pulp chamber can be contaminated with saliva, when a poor absolute isolation has been done. Also, in teeth with apical periodontitis, when the samples of study are obtained through apical surgery or tooth extractions, it is possible that the saliva or blood contaminate the samples, which leads to erroneous results.

Currently, there is a lack of knowledge about the role of viruses in endodontic diseases. Cumulative effects of virus and endopathogenic bacteria are possible; maybe the presence of viruses could promote the growth of bacteria in the apical region. Also, the activation of proinflammatory immune mechanisms can be manifested in the increase of periapical reabsorption and clinical symptoms.

The viruses can be present and replicate inside the human body without causing symptoms, so one must be careful to consider the clinical relevance of the presence of viruses. In immunocompetent patients, it is perhaps not important, but it could affect immunocompromised patients, especially EBV and HCMV, who were the most associated with the endodontic disease.

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