



Herpes Simplex Virus 1 and 2 in Chronic Periodontitis: Prevalence and Association with Clinical Parameters

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Abstract

Objective

Apart from the well-established role of bacterial plaque with periodontal disease, several studies have reported a possible role of herpes viruses in the pathogenesis and progression of periodontal disease. The purpose of this study was to determine the prevalence of Herpes Simplex Virus types 1 and 2 (HSV-1 and HSV-2) in chronic periodontitis patients and healthy subjects and to associate viral presence with clinical parameters.

Methods

Subgingival plaque samples were harvested from 26 chronic periodontitis patients (CP group) and 11 healthy subjects (H group). One pooled sample from the mesial sites of molar teeth, one sample from the deepest pocket and one sample from a gingivitis site were collected from the CP patients. Each H subject contributed with one pooled sample from the mesial sites of molar teeth. Clinical parameters were recorded in both groups. Nested PCR was employed for viral detection. A chi-square test was used to compare detection frequencies of the viruses between groups and differences in clinical parameters were evaluated by a t-test.

Results

HSV-1 was detected in 42.3% of the CP and 27.3% of the H subjects ($p>0.05$). HSV-2 was detected in 30.8% and 18.2% of the CP and H participants, respectively ($p>0.05$). Regarding the sampling site, the detection frequency of both viruses was similar between the CP and H pooled samples and between the deepest pockets and gingivitis sites within the CP group. HSV-1 was inversely correlated with periodontal pocket depth ($p=0.012$). HSV-2 was not associated with any clinical parameter.

Conclusions

These results do not support a possible role of HSV-1 and HSV-2 in the pathogenesis of chronic periodontitis.

Keywords

Chronic periodontitis; Dental plaque; Herpes virus 1; Herpes virus 2

Introduction

Periodontitis is an infectious disease of the tooth supporting periodontal structure, characterised by the progressive destruction of connective tissue attachment, alveolar bone resorption and finally, if left untreated by tooth loss. Initiation and progression of periodontitis depends on microbial and local environmental determinants, in conjunction with the complex host immune response [1,2]. Although the periodontopathogenic role for certain bacteria including *Porphyromonas gingivalis*, *Tanarella forsythia* and *Treponema denticola* is already well established, [3] new taxa such as *Filifactor alocis* and *Synergistetes* have been implicated, [4] providing new insight into the complexity of subgingival microbial communities. However, microorganisms alone cannot shed light on certain clinical aspects of the periodontal disease, including the localised pattern of periodontal breakdown, the intermittent periods of exacerbation and remission and the conversion of the stable periodontal status to disease-active periodontitis [5].

Several studies have demonstrated a positive association between human cytomegalovirus (HCMV), Epstein Barr (EBV), Herpes Simplex Virus (HSV) and chronic periodontitis [6-8]. In addition, herpes viruses are detected frequently in aggressive periodontitis, [9] acute necrotizing ulcerative gingivitis, [10] periodontal abscess, [11] HIV-associated periodontitis, [12] periimplantitis [13] and some types of periodontitis associated with systemic diseases [14,15]. According to the pathogenic model for periodontitis proposed by Slots and Contreras (2000), periodontal pathology may be the result of either a direct cytopathic effect due to virus infection and replication or a virally mediated impairment of host defense, leading to increased virulence of pathogenic bacteria [16].

Herpes simplex viruses 1 and 2 (HSV-1 and HSV-2) belong to the alpha Herpesviridae subfamily and can give rise to oropharyngeal and genital infections. After primary infection, these HSV establish latency in sensory neurons, and can be reactivated by injury, physical or emotional stress, exposure to UV-light, immunosuppressive drugs, fever and hormonal changes [17]. The potential role of HSV in the pathogenesis of periodontal disease has been investigated and the findings were rather conflicting. Some studies have shown a higher prevalence of HSV in chronic periodontitis patients compared to healthy subjects, [8,18] while other studies have failed to demonstrate similar results [19-22]. Furthermore, HSV has been positively correlated with increased periodontal pocket depth and loss of attachment in chronic periodontitis patients [23,24].

In an attempt to further elucidate the relationship between HSV and periodontitis, the present study aimed to compare the prevalence of HSV-1 and HSV-2 in sub gingival plaque samples from patients with chronic periodontitis to those from periodontally healthy individuals and to determine if possible the association between viral detection and clinical parameters.

Materials and Methods

Study design

The study protocol was approved by the Ethics Committee of the School of Dentistry at National and Kapodistrian University

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of Athens (approval number 307). The study was conducted in full accordance with the World Medical Association Declaration of Helsinki. All subjects participating in this study were referred to the Postgraduate Clinic at the Department of Periodontology, School of Dentistry, National and Kapodistrian University of Athens, for periodontal treatment or management of mucogingival problems. Participants were allocated in two groups: eleven healthy subjects (H group) and twenty-six patients suffering from advanced chronic periodontitis (CP group), according to the 1999 Classification. Each participant provided written informed consent.

Each periodontitis patient exhibited at least four ≥ 5 mm probing pocket depths, clinical attachment loss ≥ 4 mm in at least three different quadrants, bleeding on probing and radiographic evidence of bone loss. Healthy subjects showed no evidence of gingival inflammation and had no history of periodontitis. Exclusion criteria included systemic diseases, medication affecting the periodontium, pregnancy or lactation, systemic antibiotic treatment during the last 3 months, periodontal treatment during the last 6 months and <20 teeth present. Additionally, participants presenting with an active oral herpes virus infection during sampling were excluded in order to avoid cross-contamination of the periodontal tissues from the active site of infection.

Clinical examination and subgingival plaque collection

A thorough clinical and radiographic examination was performed for all participants during their first visit to the clinic to evaluate their periodontal status. The following clinical measurements were recorded: Plaque Index (PI) [25] and Gingival Index Simplified (GIS) [26] at four sites per tooth (mesial, distal, buccal, lingual), and bleeding on probing (BOP), periodontal pocket depth (PPD) and clinical attachment loss (CAL) at six sites per tooth.

On a different session, subgingival plaque samples were obtained from both groups. In the CP group, each patient contributed with three subgingival plaque samples: one pooled sample from the mesial sites of molar teeth, one sample from the deepest pocket of the dentition and one sample from a gingivitis site (probing depth ≤ 3 mm). In the H group, one pooled sample from the mesial sites of molar teeth was collected from each subject. In total, 78 CP samples and 11 H samples were evaluated. A sterile periodontal curette was used for the subgingival plaque collection. Prior sampling, the sites were isolated with cotton rolls and cleaned from supragingival plaque and saliva using sterile gauze and air-dried. The curette was inserted in the pocket or sulcus and subgingival plaque samples were obtained by a single stroke. Each participant was then scheduled for the appropriate periodontal procedure according to the treatment plan.

The samples were stored in Eppendorf tubes suspended in RNA Later (Thermo Fisher Scientific, Waltham, MA, USA) at -20°C until processed.

DNA extraction and PCR procedures

The plaque samples were centrifuged at 13500 rpm for 15 min and the supernatant was removed. Nucleic acid was extracted using the DNeasy Blood and Tissue kit (Qiagen, Hilden, Germany) following manufacturer's instructions. The nested PCR method was employed to detect viral DNA. The specific primers for HSV-1 and HSV-2 are described in Table 1. The sensitivity threshold of the nested PCR was established by amplifying 10-fold dilutions of viral DNA. PCR was performed with a final volume of 25 μl mixture containing 5 pmol each primer, 1 U Taq DNA polymerase (Invitrogen, Thermo Fisher Scientific), 1.5 mM MgCl_2 , 2.5 μl of 10x Taq buffer, 0.2 mM each deoxynucleotide triphosphate and 3 μl of DNA template or 1.5 μl of PCR product in the first or second amplification round, respectively. Briefly, the PCR conditions included an initial denaturation step at 94°C for 3 min, followed by 40 cycles of denaturation at 94°C for 30 s, primer annealing at annealing temperature for 30 s (Table 1) and extension at 72°C for 30 s, and then a final extension step at 72°C for 7 min. Positive and negative controls were included in each experiment. All samples were tested in duplicate. Amplicons were electrophoresed on 2% agarose gels, stained with ethidium bromide (0.5 $\mu\text{g}/\text{ml}$) and observed under an ultraviolet light transilluminator.

Statistical analysis

The median age of CP patients and healthy subjects were compared with the Mann-Whitney test. The Pearson's chi-square test for independence testing confirmed by Fisher's exact probability was performed to compare the groups with regard to gender, smoking habits and frequency of viral detection. To evaluate differences in clinical parameters between positive and negative CP patients, the Mann-Whitney test was used. The SPSS 22.0 version (IBM, Armonk, NY, USA) was used for the statistical analysis of the results and p values <0.05 were considered statistically significant.

Results

The demographic data of the participants are presented in Table 2. Twenty-six individuals were diagnosed with chronic periodontitis, while 11 subjects were classified as periodontally healthy. The groups were equivalent with regard to gender. The CP group included higher proportions of smokers although not statistically different to the H group. Patients in the CP group were significantly older than those in the H group ($p < 0.05$).

According to our findings, 11 (42.3%) CP patients and 3 (27.3%) healthy subjects were positive for HSV-1 ($p = 0.48$), while HSV-2 was detected in 8 (30.8%) CP patients and 2 (18.2%) healthy subjects ($p = 0.69$). Coinfection was found in 6 (23.1%) CP patients. Despite the higher prevalence of both viruses in the CP group on a subject basis, these differences were not statistically significant. The detection

Table 1: PCR primer sequences of HSV-1 and HSV-2.

Virus	Primer pairs	Nucleotide Sequence 5'-3'	Annealing Temperature	Reference
HSV-1	Outer	TACATCGCGCTCATCTACGGGG	56°C	[27]
		GGGCCAGGCGCTTGTTGGTGTA		
	Inner	GCGTTTATCAACCGCACCTCC	57°C	
		CAGTTCGGCGGTGAGGACAAA		
HSV-2	Outer	ACGTACTACCGGCTCAC	58°C	[28]
		CCACCTTACCCACAAC		
	Inner	CCGCGCCTGCCGTGAGCCATCCTC	59°C	
		AGACCCACGTGCAGCTCGCCG		

rate of viral DNA in sub gingival plaque samples is reported in Table 3. When all the examined sites in the CP group were analyzed, HSV-1 and HSV-2 were detected in 12 (15.4%) and 10 (12.8%) of the samples, respectively. These percentages were even lower than those observed in the H group. Stratification according to sampling site did not reveal significant differences in viral frequency between the CP and H pooled samples or between the deepest pockets (PPD \geq 7 mm) and gingivitis sites within the CP group.

The correlation between the clinical parameters of CP patients and viral detection is shown in Table 4. No significant differences were observed between positive and negative patients for HSV-1 with regard to GI-S, BOP and CAL. A trend towards lower PI was found in the HSV-1 positive subgroup compared to the negative subgroup (p=0.068). Moreover, PPD was statistically lower in HSV-1 positive patients compared to HSV-1 negative patients (p=0.012). HSV-2 was not correlated with any clinical parameter, although lower PPD values were observed as well in positive patients. Detection rate of both viruses showed no age predilection (data not shown) and it was similar between smokers and non-smokers in the CP group.

Discussion and Conclusion

In the present study, we attempted to evaluate the prevalence of HSV-1 and HSV-2 in subgingival plaque samples of patients with chronic periodontitis and periodontally healthy subjects and to investigate the possible association between the virus detection and the clinical parameters in the periodontitis patients.

In several studies, the association between herpes viruses and periodontal diseases has been investigated with the researchers mainly focusing on the presence of common sequences of HSV [8] or the subtype HSV-1 [20] in chronic periodontitis. In our study, we provide the detection frequencies of both subtypes HSV-1 and HSV-

2 in a Greek population by using specific primers. The nested PCR technique was used for viral detection due to its increased sensitivity.

According to our findings, 42.3% of the patients and 27.3% of the controls were positive for HSV-1 and HSV-2 was detected in 30.8% and 18.2%, respectively. A statistically significant higher prevalence of any virus in the CP group compared to the H group was not observed. Although the participants in the H group were younger than the patients in the CP group, this difference did not interfere with our results, since first infection by HSV-1 or HSV-2 occurs mainly at an early age [17]. Because the pooling of samples might overestimate viral presence, we analysed plaque samples from deep pockets and gingivitis sites as well. In our study, the detection rate for HSV-1 and HSV-2 did not differ between the pooled samples of the CP group and those of the H group. Additionally, both herpes viruses were detected with similar frequency in the deepest pockets and the gingivitis sites. In accordance with our results, Imbronito et al. detected HSV-1 in subgingival plaque in the 40% of patients with moderate to severe chronic periodontitis and in the 20% of healthy subjects [20]. On the contrary, in the study of Nishiyama et al., the HSV-1 detection rate was 46.4% in periodontal pockets from chronic periodontitis patients, while none of the healthy controls were HSV-1 positive [18]. Contreras & Slots have shown a 100% prevalence of HSV-1 in gingival crevicular fluid (GCF) samples obtained from patients with chronic periodontitis, with juvenile periodontitis, with HIV-associated periodontitis and from healthy gingival sites in periodontally diseased adults; whilst they failed to detect HSV-2 in the samples [19].

Ethnic heterogeneity must be considered, since in American and Asian populations herpes viruses have been associated with periodontal disease [18,27-31], while studies with a Caucasian population showed contradictory results [21,24]. Discrepancies between studies may also be explained by the different sampling methodology used. In our study, we used subgingival plaque by

Table 2: Demographic data of chronic periodontitis patients and healthy subjects.

Variable	H group (n=11)	CP group (n=26)	P-value
Age (yr; mean \pm SD)	30.7 \pm 7.5	50.8 \pm 10.8	<0.005
Females (%)	72.72%	61.53%	0.71
Smokers (%)	36.36%	61.53%	0.28

Table 3: Detection frequencies of HSV-1 and HSV-2 in subgingival plaque samples.

	CP group				H group
	Pooled samples (n=26)	Deep pocket (n=26)	Gingivitis site (n=26)	Total CP samples (n=78)	Pooled samples (n=11)
HSV-1	4 (15.4%)	3 (11.5%)	5 (19.2%)	12 (15.4%)	3 (27.3%)
HSV-2	3 (11.5%)	4 (15.4%)	3 (11.5%)	10 (12.8%)	2 (18.2%)

Note: HSV-1 detection: Total CP versus H p=0.39, Pooled CP versus H p=0.40, Deep pockets versus gingivitis sites p=0.70

HSV-2 detection: Total CP versus H p=0.64, Pooled CP versus H p=0.62, Deep pockets versus gingivitis sites p=1.00

Table 4: Relationship between clinical parameters of chronic periodontitis patients and viral presence.

Clinical parameter	HSV-1			HSV-2		
	positive patients (n=11)	negative patients (n=15)	p value	positive patients (n=8)	negative patients (n=18)	p value
Smokers (%)	63.63%	60%	0.85	50%	66.67%	0.42
PI (%)	66.78 \pm 17.38	81.32 \pm 18.50	0.068	74.17 \pm 23.90	72.59 \pm 17.63	0.96
GI-S (%)	44.11 \pm 24.05	62.16 \pm 29.68	0.09	58.37 \pm 32.93	51.07 \pm 26.62	0.51
BOP (%)	63.22 \pm 27.90	73.87 \pm 12.75	0.52	63.63 \pm 35.41	67.04 \pm 16.57	0.56
PPD (mm)	4.86 \pm 0.41	5.28 \pm 0.41	0.012*	4.93 \pm 0.29	5.24 \pm 0.51	0.09
CAL (mm)	4.90 \pm 1.45	5.05 \pm 1.52	0.70	4.32 \pm 0.99	5.00 \pm 1.35	0.44

Note: Values are given as mean \pm SD; * Statistically significant P<0.05

curette as a sampling method, which can yield a substantial amount of DNA for viral detection, but also HSV infected cells from the sulcular epithelium [32]. Subgingival plaque collected by curette [21], GCF by collected paper points [29], gingival tissue biopsies [30] and saliva [33] have served as reliable sources for the study of herpes virus presence in periodontal disease. It is worthy to note although that Contreras et al. demonstrated positive association between HSV and chronic periodontitis in the gingival biopsy samples, but not in the GCF samples [30].

Concerning the clinical parameters, patients positive for HSV-1 presented with significantly lower PPD and a trend towards decreased PI. The studies of Ling et al. and Petrovic et al. reported also lower PI scores in chronic periodontitis patients positive for HSV [23,24]. However, these studies demonstrated a positive association between the presence of HSV and increased pocket depth and clinical attachment loss. Furthermore, Saygun et al. found that HSV correlated with higher plaque index and gingival index in chronic periodontitis patients [19].

To the knowledge of the authors, for the first time an inverse correlation between HSV-1 detection and PPD is reported. The immunological aspects of HSV biology should be taken into account. It seems that HSV can develop several mechanisms in order to evade the host immune response. There is evidence that HSV can be detected in T-lymphocytes and monocytes/macrophages from chronic periodontitis lesions [34]. HSV-infected cells may be protected by antibody and complement-mediated lysis [35] and they demonstrate a reduced expression of MHC class I antigens [36]. Furthermore, HSV may impair functions of macrophages and neutrophils, as well as disarm natural killer cells [37-39]. Moreover, HSV can down regulate the expression of proinflammatory cytokines by interfering with the NF-kb pathway [40]. These evasion 'strategies' could counteract the periodontal breakdown caused by the immune response to bacterial infection and thus it might explain the decreased periodontal pocket depth observed in HSV-1 positive CP patients. However, these speculations should be investigated and confirmed by future studies.

In conclusion, HSV-1 and HSV-2 were detected with similar frequency in chronic periodontitis patients and periodontally healthy subjects. A clinical relevance of herpes virus infection in chronic periodontitis could not be confirmed.

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