Association between human herpes virus and aggressive periodontitis: A systematic review

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Received 2 March 2016; revised 19 May 2016; accepted 17 June 2016

OBJECTIVES: to elucidate the association between HHVs [Human Herpes Viruses–human cytomegalovirus (HCMV), Epstein–Barr virus (EBV) and herpes simplex virus (HSV)] and risk of aggressive periodontitis (AgP) and advanced periodontitis (AP).

MATERIALS AND METHODS: the addressed focused question was: “Is there an association between HHVs and AgP and do HHVs implicate in the pathogenesis of AgP and AP?” Electronic search of the MEDLINE/PubMed, EMBASE, Scopus, ISI Web of knowledge, and Google-Scholar databases was combined with hand searching of articles published from 1970 up to and including March 2016 using relevant MeSH terms. Review papers, in-vitro and experimental studies, case reports, commentaries, interviews, updates and duplicate publications were excluded. Results: twelve studies were included. Three studies reported elevated percentage of HSV1 carriage in AgP patients whereas two studies reported comparable percentage levels of HSV1 among AgP patients and periodontally healthy patients. Seven studies reported significantly higher percentage levels of HCMV in AgP patients as compared to healthy controls whereas four studies showed comparable levels of HCMV among AgP and healthy controls. Six studies reported higher EBV carriage in AgP patients than healthy controls whereas five studies showed comparable EBV percentage levels among AgP and periodontally healthy patients. Conclusion: overall, human herpes virus (HSV, CMV and EBV) levels are increased and are found to be associated with AgP and AP as compared to healthy individuals. However a possible involvement of HHVs in the pathogenesis of AgP warrants further investigation.

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Please cite this article in press as: Alzahrani AA Association between human herpes virus and aggressive periodontitis: A systematic review, The Saudi Journal for Dental Research (2016), http://dx.doi.org/10.1016/j.sjdr.2016.06.004
1. Introduction

1.1. Rationale

Aggressive periodontitis (AgP) is a rapidly progressive periodontal disease in adults associated with limited amount of dental plaque, in otherwise systemically healthy individuals. The etiopathogenesis of AgP involves multifactorial risk factors such as immunologic, genetic, and environmental factors. The current understanding of the pathogenesis of AgP suggests that it is associated with anaerobic gram-negative pathogenic bacteria such as Aggregatibacter actinomycetemcomitans (Aa), Prevotella intermedia and Porphyromonas gingivalis (Pg). However, several studies have reported that deep periodontal pockets are also associated with human herpesviruses (HHVs) and may be the source of periodontal tissue destruction. Human herpesviruses are a group of enveloped DNA viruses which belong to the family herpesviridae. The most common types of HHVs affecting humans are herpes simplex virus (HSV) type 1 and 2; cytomegalovirus (CMV); and Epstein–Barr virus (EBV). Aggressive periodontitis patients are associated with a state of elevated localized inflammatory burden due to increased gingival crevicular fluid cytokine levels. Herpesvirus infection is thought to stimulate local cytokine production through macrophages and other inflammatory cells which may lead to the impairment of local periodontal immune defense. Herpesviruses target host cells by attachment onto the cell surface through glycoproteins present in the viral envelope. A number of studies suggest that HHVs are associated with clinical periodontal parameters in AgP. These viruses with bacteria, may be implicated in causing periodontal destruction. In this context, it may be hypothesized that the subgingival carriage of herpesvirus in patients affected by AgP should be elevated as compared to periodontally healthy individuals and may be implicated in causing the disease. Moreover, what drives these viruses for causing AgP is still unclear. In the past decade, a number of microbiological studies have been conducted to elucidate the role of HHVs in the pathogenesis of AgP and advanced periodontal lesions. The present study is designed to clarify the periodontopathogenic role of HHVs in AgP and advanced periodontitis (AP).

1.2. Objective

Therefore, the aim of the present study was to elucidate the association between HHVs [Human Herpes Viruses–human cytomegalovirus (HCMV), Epstein–Barr virus (EBV) and herpes simplex virus (HSV)] and risk of AgP and AP.

2. Materials and methods

2.1. Focused question

This review was registered at the National Institute for Health Research PROSPERO, International Prospective Register of Systematic Reviews, registration number CRD42015013792. Based on the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines, a specific question was constructed. The addressed focused question was “Is there an association between HHVs and AgP and do HHVs implicate in the pathogenesis of AgP and AP?”
2. Eligibility criteria

The following eligibility criteria were entailed: case-control studies; cross-sectional studies; patients with AgP and/or AP versus healthy controls; in-vivo studies evaluating the association between herpes viruses and AgP; studies reporting prevalence of one or more human herpes viruses such as HCMV, EBV or HSV in subgingival plaque samples as outcome; studies evaluating periodontal active sites and stable sites within AgP patients only; studies published in English language only.

The exclusion criteria included: review papers, in-vitro and experimental studies, case reports, commentaries, interviews, updates and duplicate publications.

2.3. Data sources

The author (AAA) searched the MEDLINE/PubMed, EMBASE, Scopus, ISI Web of knowledge, and Google-Scholar databases from 1970 up to and including March 2016 for appropriate articles addressing the focused question. A structured approach to literature searching was used to identify the relevant papers that report the prevalence of HHVs in AgP patients. Reference lists of original studies were hand...
<table>
<thead>
<tr>
<th>Author et al., year</th>
<th>Study design; population</th>
<th>Sample size; percentage female</th>
<th>Mean age in years (range)</th>
<th>Study groups</th>
<th>Mean Pocket depth</th>
<th>Mean Clinical attachment level</th>
<th>Main outcomes</th>
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</thead>
<tbody>
<tr>
<td>Sharma et al., 2015</td>
<td>Cross-sectional; India</td>
<td>30; 50%</td>
<td>23.3</td>
<td>AgP: 15; Control: 15 (NA)</td>
<td>NA</td>
<td>NA</td>
<td>– HCMV was significantly higher in AgP group than healthy controls – EBV was comparable among both the groups – EBV was significantly higher in AgP group than healthy controls – HSV1 and HCMV were comparable among both groups – HSV1 and EBV were significantly higher in AgP group than in controls – HSV2 and HCMV were comparable among both groups</td>
</tr>
<tr>
<td>Dani et al., 2013</td>
<td>Cross-sectional; India</td>
<td>30; 43%</td>
<td>22.77</td>
<td>AgP: 15; Control: 15 (18–30)</td>
<td>3.56 ± 1.12 Control: 1.36 ± 0.19</td>
<td>AgP: 2.33 ± 1.40 Control: –</td>
<td>– HSV1 and HCMV were comparable among both groups</td>
</tr>
<tr>
<td>Das et al., 2012</td>
<td>Cross-sectional; India</td>
<td>10; 60%</td>
<td>18.1–55</td>
<td>NA: 25; Control: 25</td>
<td>NA</td>
<td>NA</td>
<td>– HSV1 and EBV were significantly higher in AgP group than in controls – HSV2 and HCMV were comparable among both groups</td>
</tr>
<tr>
<td>Sharma et al., 2012</td>
<td>Case-control; India</td>
<td>60; 48%</td>
<td>29.65</td>
<td>AgP: 20; Control: 20 (20–45)</td>
<td>8.91 ± 0.93 Control: 0.75 ± 0.56</td>
<td>AgP: 8.32 ± 0.96 Control: –</td>
<td>Both HCMV and EBV were significantly higher in AgP groups than healthy controls</td>
</tr>
<tr>
<td>Botero et al., 2007</td>
<td>Case-control; Colombia</td>
<td>52; 69%</td>
<td>24.3</td>
<td>AgP: 10; Control: 22 (NA)</td>
<td>4.24 ± 0.42 Control: 2.55 ± 0.32</td>
<td>AgP: 3.97 ± 0.46 Control: 2.52 ± 0.3</td>
<td>– HSV1 and EBV were significantly higher in AgP group than in controls – HSV2 and HCMV were comparable among both groups – HSV1 and HCMV were significantly higher in active sites than stable sites in AgP group – HSV2 and EBV were comparable among both active and stable sites in AgP</td>
</tr>
<tr>
<td>Imbronito et al., 2008</td>
<td>Case-control; Brazil</td>
<td>120; 61%</td>
<td>27.3</td>
<td>AgP: 30; Control: 30 (NA)</td>
<td>4.3 ± 0.4 Control: 2.0 ± 0.2</td>
<td>AgP: 4.8 ± 0.4 Control: 2.1 ± 0.2</td>
<td>– HSV1 and EBV were significantly higher in AgP group than in controls – HSV2 and HCMV were comparable among both groups – HSV1 and EBV were significantly higher in AgP group than in controls</td>
</tr>
<tr>
<td>Kamma et al., 2001</td>
<td>Cross-sectional; Greece</td>
<td>16; 44%</td>
<td>33.1; (NA)</td>
<td>Active sites: 32; Stable sites: 32</td>
<td>Active sites: 6.8 ± 1.6 Stable sites: 5.6 ± 1.3</td>
<td>Active sites: 6.9 ± 1.4 Stable sites: 5.6 ± 1.6</td>
<td>– HSV2 and EBV were significant</td>
</tr>
<tr>
<td>Nibali et al., 2009</td>
<td>Case-control; United Kingdom</td>
<td>140; 59%</td>
<td>33.5</td>
<td>AgP: 80; Control: 40 (NA)</td>
<td>LAgP: 3.5 ± 0.6 GAgP: 4.0 ± 0.9</td>
<td>LAgP: 3.8 ± 0.5 GAgP: 4.2 ± 1.0</td>
<td>– HSV1, HCMV and EBV were significantly higher in AgP group than healthy controls – HSV2 was comparable among both groups</td>
</tr>
<tr>
<td>Saygun et al., 2004</td>
<td>Cross-sectional; Turkey</td>
<td>34; 50%</td>
<td>24.1</td>
<td>AgP: 18; Control: 16 (17–31)</td>
<td>5.0 ± 1.1 Control: 2.1 ± 0.6</td>
<td>AgP: 5.1 ± 1.1 Control: 2.1 ± 0.6</td>
<td>– HSV1, HCMV and EBV were significantly higher in AgP group than healthy controls – HSV2 was comparable among both groups</td>
</tr>
<tr>
<td>Stein et al., 2013</td>
<td>Cross-sectional; Germany</td>
<td>130; 57%</td>
<td>24.1</td>
<td>AgP: 65; Control: 65 (23–70)</td>
<td>5.8 ± 1.2 Control: 2.8 ± 0.3</td>
<td>AgP: 6.7 ± 1.6 Control: 3.1 ± 0.5</td>
<td>– HSV1, HCMV and EBV were comparable among both groups</td>
</tr>
<tr>
<td>Ting et al., 2000</td>
<td>Cross-sectional; United States</td>
<td>11; 63%</td>
<td>NA (10–23)</td>
<td>3 active sites</td>
<td>NA</td>
<td>NA</td>
<td>– HSV2 and HCMV were comparable among both groups</td>
</tr>
<tr>
<td>Yapan et al., 2003</td>
<td>Prospective; Turkey</td>
<td>33; 42%</td>
<td>24.05</td>
<td>AgP: 17; Control: 16 (17–31)</td>
<td>5.08 ± 1.07 Control: 1.71 ± 0.39</td>
<td>AgP: 5.04 ± 1.13 Control: 1.71 ± 0.39</td>
<td>– HSV1, HCMV and EBV were significantly higher in AgP group than healthy controls – HSV2 and HCMV were comparable among both groups – HSV1, HCMV and EBV were significantly higher in AgP group than healthy controls – HSV2 and HCMV were comparable among both groups</td>
</tr>
</tbody>
</table>

AgP: aggressive periodontitis, HSV: herpes simplex virus, HCMV: human cytomegalovirus, EBV: Epstein–Barr virus, NA: not available.

§ Type of HSV not specified.

Y: Split-mouth technique having test and control periodontal sites in same subjects.
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3. Results

3.1. Study selection

The search protocol is presented in Fig. 1. A total of 42 studies were initially identified. After screening of the titles and abstracts, 30 papers were excluded and a total of 12 papers7,12,13,15,17–24 were included in the systematic review (Table 1). All studies7,12,13,15,17–24 were performed at either universities or health care centers. Fig. 1 shows the study identification flow with the reasons for exclusion of articles.

3.2. General characteristics of the studies included

Twelve studies7,12,13,15,17–24 included in the present review enlisted seven cross-sectional studies7,12,13,15,17–19,22,23, four case-control studies20,21,24 and one prospective intervention study13 (Table 1). The total number of participants in the included studies ranged between 1018 and 14023 individuals with mean age ranging between 23.1318 and 50.324 years. All the included studies7,12,13,15,17–24 reported percentage of female participants, which ranged between 42.15 and 69.21 individuals. The number of AgP patients ranged from 1021 and 8024 whereas healthy control patients ranged between 140 to 80.24 respectively. The mean pocket depth (PD) and clinical attachment level (CAL) in AgP patients ranged from 3.5 ± 0.6 to 8.91 ± 0.93 and 2.33 ± 1.4 to 8.32 ± 0.96 respectively. All studies7,12–14,16–23 collected subgingival plaque samples either with the help of curette13,17,20,23,25 or paper points7,12,15,21,22. Three types of herpesviruses including HSV, HCMV and EBV were studied in all the included studies7,12,13,15,17–24. All studies7,12,13,15,17–24 employed polymerase chain reaction (PCR) technique for the detection of herpesviruses (see Table 2).

3.3. Main outcomes of the included studies

3.3.1. Herpes simplex virus

Seven7,12,15,18,19,22,23 out of 12 studies included7,12,13,15,17–24 evaluated the percentage levels of HSV in AgP and periodontally healthy controls. Three studies19,23 reported elevated percentage of HSV1 carriage in AgP patients whereas two studies15,18 reported comparable percentage levels of HSV1 among AgP patients and periodontally healthy patients. Two studies15,24 showed comparable percentage levels of HSV2 among AgP patients and healthy controls. HSV1 in AgP and periodontally healthy patients ranged from 1.5% to 86.7% and 0% to 20% respectively whereas, HSV2 in AgP and healthy controls ranged from 8% to 16.7% and 0% to 4% respectively.

Two studies12,22 reported prevalence of HSV in AgP and healthy controls without differentiated into type 1 and type 2.

3.3.2. Cytomegalovirus

All the studies evaluated the percentage levels of HCMV in AgP patients and healthy controls. Seven studies reported significantly higher percentage levels of HCMV in AgP patients as compared to healthy controls whereas four studies showed comparable levels of HCMV among AgP and healthy controls. One study did not detect HCMV in either groups. The percentage levels of HCMV in AgP and healthy controls ranged from 0% to 27.2% and 0% to 56.7% respectively.

3.3.3. Epstein–Barr virus

Epstein–Barr virus was studied in overall eleven studies.7,12,13,15,17–20,22,24 Six studies7,13,18–20,23 reported higher EBV carriage in AgP patients than healthy controls whereas five studies15,17,19,22,24 showed comparable EBV percentage levels among AgP and periodontally healthy patients. The percentage levels of EBV in AgP and healthy controls ranged from 7.5% to 72.2% and 0% to 18.1% respectively.

3.3.4. Advanced periodontitis

Advanced periodontitis lesions are comprised of deep pocket depths ≥ 6mm. Deep pockets were associated with prevalence of HHVs in advanced form of lesions. Subjects with advanced form of periodontitis were seen in three studies.15,20,22 The mean pocket depth ranged from 6.8 mm to 8.9 mm.

4. Discussion

The present study was based on the hypothesis that HHVs including, HSV1, HSV2, CMV and EBV levels would be significantly raised in AgP patients as compared to individuals with healthy periodontium. Overall, the levels of HHVs were raised in AgP as compared to healthy subjects in the studies reviewed.12,13,15,17–24 The results of this study is corroborated by previous literature review by Rodrigues et al.14 which showed positive association between HHVs and AgP. Aggressive periodontitis is characterized by early onset, rapid periodontal tissue destruction and little presence of plaque. Although specific pathogens including Fusobacterium nucleatum (Fn), Pg and Aa are implicated in its pathogenesis, it is unlikely that a small group of bacteria are responsible for this heterogeneous disease.22 The simultaneous occurrence of
<table>
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<tr>
<th>Author et al., year</th>
<th>Type of sample</th>
<th>Sampling method</th>
<th>Microbiological analysis</th>
<th>Sampled site</th>
<th>Herpesviruses Prevalence (%)</th>
<th>HCMV (+)</th>
<th>EBV (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
<td>HSV(+) Test Control</td>
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<tr>
<td>Sharma et al., 2015</td>
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<td>Curette</td>
<td>Hotstart PCR</td>
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<td>Multiple PCR</td>
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<td>HSV1 = 13.0</td>
<td>53.0</td>
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<td>Curette</td>
<td>Multiple PCR</td>
<td>≥6 mm PD</td>
<td>HSV1 = 80</td>
<td>HSV1 = 12</td>
<td>12.0</td>
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<td>Curette</td>
<td>PCR</td>
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<td>HSV2 = 4</td>
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<td>Nested PCR</td>
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<td>NA</td>
<td>HSV1 = 80</td>
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<td>Subgingival plaque</td>
<td>Paper point</td>
<td>Nested PCR</td>
<td>HSV1 = 86.7</td>
<td>HSV1 = 20.0</td>
<td>60.0</td>
<td>56.7</td>
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<td>Kamma et al., 2001</td>
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<td>NA</td>
<td>HSV1 = 86.7</td>
<td>59.4*</td>
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<td>Nibali et al., 2009</td>
<td>Subgingival plaque</td>
<td>Curette</td>
<td>Real-time PCR</td>
<td>≥5 mm PD</td>
<td>NA</td>
<td>HSV1 = 77.8</td>
<td>72.2*</td>
</tr>
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<td>Saygun et al., 2004</td>
<td>Subgingival plaque</td>
<td>Curette</td>
<td>PCR</td>
<td>HSV1 = 17.8</td>
<td>HSV1 = 0</td>
<td>HSV1 = 17.8</td>
<td>72.2*</td>
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<tr>
<td>Stein et al., 2013</td>
<td>Subgingival plaque</td>
<td>Paper point</td>
<td>Real-time PCR</td>
<td>HSV1 = 15.7</td>
<td>HSV1 = 0</td>
<td>HSV1 = 15.7</td>
<td>1.5</td>
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<td>Ting et al., 2000</td>
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<td>Paper point</td>
<td>Nested PCR</td>
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<td>HSV1 = 0</td>
<td>HSV1 = 15.7</td>
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<td>Curette</td>
<td>PCR</td>
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<td>HSV1 = 0</td>
<td>HSV1 = 15.7</td>
<td>1.5</td>
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* Statistically significant, PCR; polymerase chain reaction, HSV; herpes simplex virus, HCMV; human cytomegalovirus, EBV; Epstein–Barr virus, NA; not available.
HHVs along with Pg and Aa, has led investigators to believe that HHVs influence the occurrence and extent of AgP. It is therefore, suggested that herpes virus infection along with the inflammatory response triggers periodontal tissue destruction in periodontal disease. The release of pro-inflammatory cytokines potentially activate matrix metalloproteinase and osteoclasts causing the pathogenesis of periodontal disease. 

Interestingly, in six12,15,18,19,22,23, four15,18,19 and five12,15,17,22,24 studies, included in the present review, HSV, CMV and EBV were found to have comparable levels among sub gingival plaque of AgP and healthy subjects respectively. Multiple explanations can be presented in this regard. It has been suggested that paper points when utilized for sample collection fail to collect enough sample from the apical parts of the pockets, where viruses are expected to be in abundance.27 By contrast sample collection through curettes provide plaque from the entire pocket. In the present review, five studies7,12,15,21,22 used paper points for collection of plaque samples for assessment of viruses. This could have possibly affected the outcomes in these studies.7,12,15,21,22 In addition, the type of PCR testing has a potential influence on the detection of viral strains. It is reported that nested PCR testing is highly sensitive as compared to real time PCR in detecting viruses including CMV. In a study comparing nested with real time PCR, it was concluded that real time PCR may have provided an underestimation of viral presence.28,29 Moreover, nested PCR being highly sensitive has resulted in increased numbers of viruses detection.7,12,15,21,22 However other studies using methods including identification of 100 genome copies, have shown low levels of viruses.28,30 In addition both the nested and real time PCR fail to inform about the latency of the viruses, as viral infections tend to have asymptomatic and active phases of disease.2 It is noteworthy, that four12,15,21,22, two15,22 and two18,19 studies in the present review, used nested, real time and multiple PCR respectively, for viral strain detection. Hence, heterogeneity in methodology of the included studies could have resulted in the comparable levels of HHV among the studies reviewed.7,12,13,15,17–24 Therefore, further studies with standardized methodology, using sensitive, specific, robust and reproducible viral detection process for the identification of HHVs in subjects with AgP are recommended.

Interestingly, the prevalence range of CMV, HSV and EBV in AgP subjects as reviewed from the included studies7,12,13,15,17–24 were 0% to 72.7%, 1.5% to 86.7% and 7.5% to 72.2% respectively. These variations in the frequency of HHVs makes it challenging to correlate the presence of particular viruses (HSV, CMV, EBV) to the disease process of AgP. A possible explanation for these findings could be related to latency in herpes virus infections and the disease activity of the plaque sample sites. It has been reported that higher HHV frequency were found in active periodontal disease pockets as compared to stable sites.25 In the present review, the mean periodontal pocket depth values among the included studies in AgP patients ranged from 3.5 to 8.9 mm, eluding to the fact that the disease activity among the subjects varied considerably. This is a possible reason for the wide variations of HHV frequencies among the studies reviewed.7,12,13,15,17–24 In addition, difference in ethnicity and population subgroup may also explain the heterogeneity in the data reported. In the present review, HHV prevalence among the included studies was reported in multiple populations, including, subjects from Europe, America, Africa, South America and the Indian subcontinent. It is suggested that the distribution of genotype and prevalence of HHV in serum differs among different populations.18,31 Immune response to viral antigens is dependent on t-cell recognition. This process depends on presentation of antigen peptide by MHC (major histocompatibility complex) molecules. MHC polymorphism is ethnically influenced and therefore could influence the susceptibility toward HHV.15,32 Therefore, it is clear that the susceptibility of different populations for HHV would influence the frequency of these viruses in AgP subjects.

In the studies reviewed, it has been emphasized that the periodontal destruction in AgP patients is the outcome of a HHV and bacterial co-infection.17,22 HHV infection has the ability to impair host defense response by altering the function of chronic inflammatory and immune cells, including, macrophages, polymorphonuclear neutrophils, leukocytes and lymphocytes.10,33 In addition it is proposed that a mixed HHV infection can disrupt protective epithelial barriers, facilitating bacterial infiltration and attachment.28 This theory can be supported by explanations, that HHV co-infection with different bacteria has been observed in systemic diseases including pulmonary infections, inflammatory bowel disease, and otitis media.25 In addition, periodontal sites with co-infection of bacteria and HHV show rapid and progressive (active) periodontal destruction.25 Therefore, poorly functioning immune cells along with a weak epithelial barrier serve to augment the virulence of AgP bacterial pathogens including, Pg, Aa and Fn.

In summary, the data reviewed predict a possible influence of HHV co-infection in the progress of periodontal tissue loss in AgP patients. The HHV-bacterial association in periodontitis proposes that active HHV infection induces periodontal destruction and that inflammatory host-immune responses against the HHV infection are an important component of the etiopathogenesis of AgP. Therefore, studies identifying the effect of eradication of HHV levels for prevention and arrest of disease are recommended.

5. Conclusions

Overall, human herpes virus (HSV, CMV and EBV) levels are increased and are found to be associated with AgP and Ap as compared to healthy individuals. However a possible involvement of HHVs in the pathogenesis of AgP warrants further investigation.

Source of funding

None

Ethical approval

Not required

Conflict of interest statement

The authors declare that they have no conflict of interests and all authors have read and approved the final draft
Acknowledgements

I would like to thank Prof Sami Shafik the chairman of Preventive Dentistry Department at Riyadh Colleges of Dentistry and Pharmacy and Course directors of Master program in Periodontics for their support, motivation and willingness to help.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.sjdr.2016.06.004.

References