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VIRUS AND PERIODONTAL AREA

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Abstract:

Viral infections usually develop in 2 phases: primary infection and latent asymptomatic phase. Periods of sporadic activation between the two phases lead to viral replication, weakening of periodontal immune defenses and transmission of periodontal diseases. So-called periodontitis can be chronic, aggressive, progressive and affect probing pocket depth and clinical attachment. It all depends on the virus, the local environment and its manifestations in the oral cavity.

Objectives: Primary objective: To review how virus can be part of periodontal etiopathogenesis. Secondary objectives: To know if it exists scientific evidence between virus and the types of virus in the periodontal areas and to approach on the relation between the oral cavity and Covid 19.

Material and Methods: This research study is based on a literature review of published articles from scientific and biomedical databases. A meticulous screening was performed to evaluate the most relevant publications and answer the objectives.

Results: 8 articles were selected. HSV-1 predominant in deep pockets and in moderate disease stage. EBV more present in localized aggressive periodontitis than in generalized one. Generally, the studied viruses are present in moderate-advances lesions.

Conclusion: Generally, the immune system defenses are weaken, the virus hinders the antibacterial immune process and it leads to the growth of the periodontopathic microbiota. It's an interactive procedure between virus and bacteria in the building process of periodontal diseases. Also, virus don't work alone but usually in cooperation with other specific bacteria as periodontopathic agents in periodontal tissues destruction.(1)

Resumen:

Las infecciones víricas suelen desarrollarse en 2 fases: infección primaria y fase asintomática latente. Los periodos de activación esporádica entre ambas fases conducen a la replicación viral, al debilitamiento de las defensas inmunitarias periodontales y a la transmisión de enfermedades periodontales. La llamada periodontitis puede ser crónica, agresiva, progresiva y afectar a la profundidad de las bolsas de sondeo y a la inserción clínica. Todo depende del virus, del entorno local y de sus manifestaciones en la cavidad oral.

Objetivos: Objetivo principal: Revisar cómo los virus pueden formar parte de la etiopatogenia periodontal. Objetivos secundarios: Conocer si existe evidencia científica entre los virus y los tipos de virus en las áreas periodontales y abordar sobre la relación entre la cavidad oral y Covid 19.

Material y Métodos: Este estudio de investigación se basa en una revisión bibliográfica de artículos publicados en bases de datos científicas y biomédicas. Se realizó una selección meticulosa para evaluar las publicaciones más relevantes y responder a los objetivos.

Resultados: Se seleccionaron 8 artículos. El VHS-1 predomina en las bolsas profundas y en el estadio moderado de la enfermedad. El VEB está más presente en la periodontitis agresiva localizada que en la generalizada. En general, los virus estudiados están presentes en lesiones moderadas-avanzadas.

Conclusión: Generalmente, las defensas del sistema inmunitario están debilitadas, el virus obstaculiza el proceso inmunitario antibacteriano y conduce al crecimiento de la microbiota periodontopática. Es un procedimiento interactivo entre virus y bacterias en el proceso de construcción de las enfermedades periodontales. Además, los virus no actúan solos, sino que

suelen cooperar con otras bacterias específicas como agentes periodontopáticos en la destrucción de los tejidos periodontales.(1)

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Introduction:

Charles Darwin's theory allowed us to understand the origin and evolution of species. It states that "hereditary variation occurs slowly due to the gradual accumulation of random small modifications that are subject to natural selection". (2)

New perceptions came from viruses and microorganisms, defined as "agents that can supply genetic material into recipient cells by horizontal gene transfer (HGT)". Indeed, around two-thirds of the human genome originated from viruses. (2)(3)

Virus are considered as the most extensive organism worldwide. Although we can notice a constant progress regarding prevention and viral disease's control, the ultimate outbreaks as respiratory syndrome coronaviruses, avian influenza H7N9 viruses and Zika viruses show the persistent problem of viruses facing the health society.(3)

According to the Global Virome Project (GVP), it is estimated that there are still "over 1,67 million yet to be discovered viruses in animal reservoirs, while 631.000-827.000 of these unknown viruses can infect human". Here is the urgent need of developing efficient rapid methods in order to identify these potential human-infecting viruses.(3)

Virus have simple structure and composition but seems to go through more complex processes when they replicate in the host cell.

They initiate an infectious cycle with several steps as receptors binding and entry in cells initiating infection. Then occurs the capsid destabilization and genome uncoating. To end, they discharge viral nucleic acids ready for replication.

Recent studies demonstrated that endocytosis entry is better than direct fusion at the plasma membrane. It is used either for enveloped as for non-enveloped viruses and it is the route for virus internalization.

At the time of the initial entry, the viral attachment protein binds to a generalized receptor, better called attachment factors. As an example, Heparan sulfate proteoglycans (HSPGs) is a common factor as mean of attachment for many viruses including herpes virus, hepatitis C virus or retroviruses as human immunodeficiency virus (HIV).

The second stage of the process usually consists in receptor binding and the more critical one in terms of viral infection. Integrins are one important receptor binding for enveloped and non-enveloped viruses. Viruses as human CMV bind integrines.

Most of the changes take place on cell surface and in microtubule in charge of transport, stimulating internalization, penetration and trafficking of the new virus.

For example, the HCMV activates various signaling pathways in which the envelope glycoprotein (B) cooperates with the epidermal growth-factor receptor.

There are 2 ways of interaction with the host cells: Permissive infection with synthesis of viral components, assembly and release with death of the host cell; and non-permissive infection with cell transformation, viral replication, cell remains alive (hepatitis B, herpes viruses and retroviruses infection). (4)

Talking about virus host route entrance, we can mention 4 different ways: By inoculation (skin & mucosa) through needle sticks injury, bites or abrasions; By inhalation (respiratory tract) through aerosol or droplet; By ingestion (GI tract) through feco-oral route and by genitourinary tract through sexual activity. (4)

Anyway, the spread of infection and the viral pathogenesis require to understand the detailed process of the cellular machinery of the host. (5)

Behind all that, since recently, virus have been involved in pathogenesis of periodontal diseases. (6) Studies about the probability of periodontitis of viral origin can be looked as a turning point in this kind of researches because was more focused on the etiology of bacteria until few years ago. It is common to have a genetic polymorphism in virus of periodontal origin.(7)

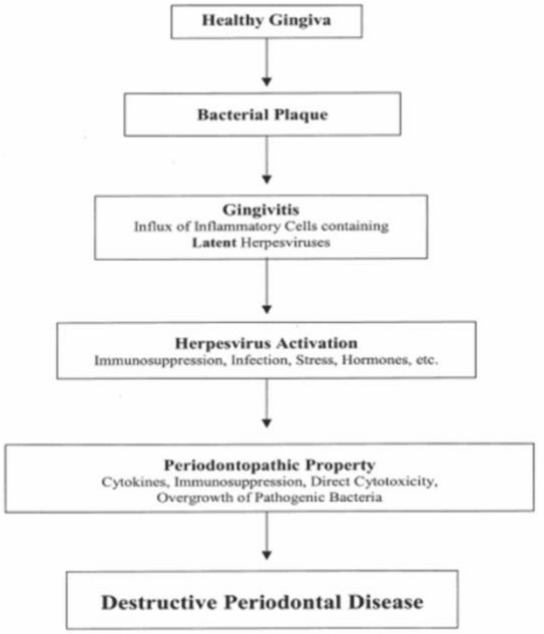
In the oral cavity, over 1200 bacterial species and 19.000 phylotypes are detected. Generally, periodontal disease has not a clear origin: either genetic or environmental in predisposed patients. The healthy periodontal areas are prone to gram positive facultative bacteria; on the other hand, periodontal lesion areas will show gram negative anaerobic species. (1)

Indeed, plaque is an crucial element in the progress of periodontitis.(4) It's a chronic disease commonly present in healthy or predisposed persons. It's multifactorial and site specific.(7) Indeed, there is great diversity in the development of this pathology. Depending on age, race, socio-economic situation, systemic conditions or habits, it would develop and progress in a very different way. (8)

Virus infections weaken periodontal defense capacities, generating subgingival overgrowth of periodontopathic bacteria. In fact, a big number of bacterial infections happens as super infections of viral diseases. Influenza is an example of that.

There is a virus-bacterium-host interaction with virus-infected periodontitis lesions an periodontopathic bacteria as mentioned just prior. As main bacteria, there are Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Dialister pneumosintes, Prevotella intermedia, Prevotella nigrescens, Treponema denticola. (4)

A good illustrative example of this synergic process with herpes virus activation leading to periodontal disease is observed with this schema. (Figure 1)(4)



Ganguly R, Pal TK.
Viruses in Periodontal Diseases

Nowadays, it is considered some types of periodontitis as a “multiple step process” implying a complex interaction between host, bacteria, viruses and environmental factors. (9)

Regarding the numerous virus involved in periodontal disease, among them, we will focus on herpes simplex virus (2 types), Human Cytomegalovirus (HHV-5) (CMV), Human Immunodeficiency Virus (HIV), human papilloma virus (HPV) and Epstein Barr Virus (EBV).(4)

Most commonly, they are DNA virus detected in gingival tissue, except HIV in this case that is a retrovirus (RNA).(10)

1) Herpes virus

This family is classified in 3 subgroups: the alpha one including herpes simplex virus 1, 2 and varicella zoster virus; The beta subgroup composed of human cytomegalovirus, herpesvirus 6 and 7; and finally the gamma one with Epstein-Barr virus and herpesvirus 8. (11)

It has been seen that over one million herpesvirus genome copies subsist in a unique periodontitis area. It impair hosts's immunity and enable the development of secondary bacterial infections.(9)

Herpesvirus initiates release of proinflammatory cytokines that will generate osteoclasts and matrix metalloproteinases activation. Then, hinders antibacterial immune process and causes growing of periodontopathic bacteria.

The association between herpes virus and aggressive periodontitis can be studied through the causal criteria of Hill. According to Hill, in order to be a causal relation between a possible risk factor and a pathology, it is required to comply with 8 postulates that will be reviewed individually and that will facilitate the determination of the role that viruses can have in the progress of periodontitis. (8)

1. Strength of the association
2. Consistence of the association
3. Specificity
4. Temporality
5. Biological gradient

6. Biological plausibility
7. Coherence
8. Experimental evidence of decrease or disappearance of the effect when the cause is suppressed.

There are close link herpesvirus-bacteria through co-infection and a bidirectional interaction.(1)

There are 2 types : HSV-1 (oral cavity) & HSV-2 (genital area). It gives skin & mucous membranes infections. The primary lesion is Herpetic gingivostomatitis with formation of vesicles in the gingiva, lips, tongue and buccal mucosa.
What we also know is that It follows a Ganglion trigger Theory or Skin trigger Theory. (4)

2) CMV

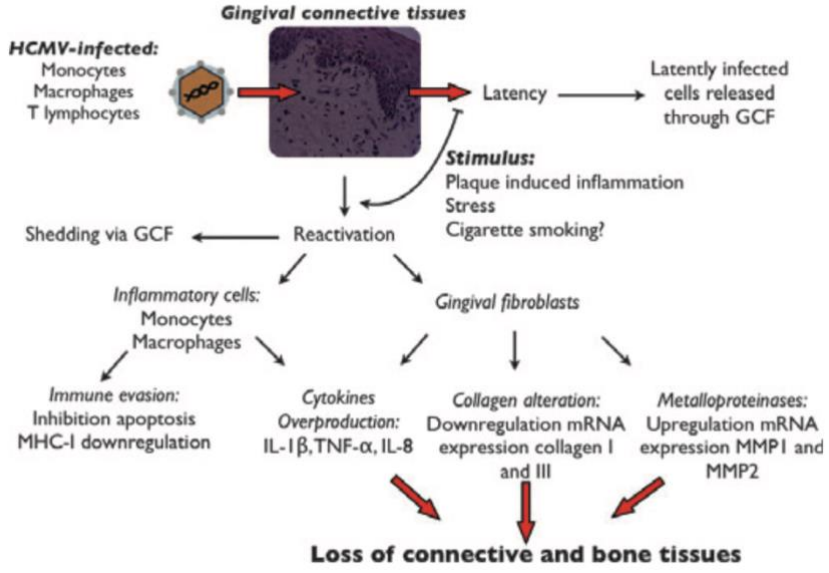
CMV is classified as the biggest genome of the human herpesviruses. It represents the most common cause of congenital and perinatal infections. It infects many different epithelial cells, endothelial cells, mesenchymal cells, hepatocytes, granulocytes and macrophages. It is found in different body secretions: saliva, urine, semen and breast milk and responsible for cytomegalo virus inclusion disease and mononucleosis. (3) (11)

Human CMV activates various signaling pathways by way of interaction between its envelope glycoprotein and the epidermal growth-factor receptor. (5)

CMV is usually present in apical and marginal periodontitis, as well in periapical cysts. When the disease is active, it is associated with an active periodontitis disease. The involvement of macrophages and T cells engage CMV into the development of periodontitis process and

further infections. It has been documented that there is a predominance of serum IgG acting against CMV in periodontitis cases than in gingivitis cases. However, the association is still not familiar. (11)

The next schema shows the cascade of events involved in the periopathogenesis of CMV. (Figure 2) (11). It is going along with a diminution of host and cellular immunity.

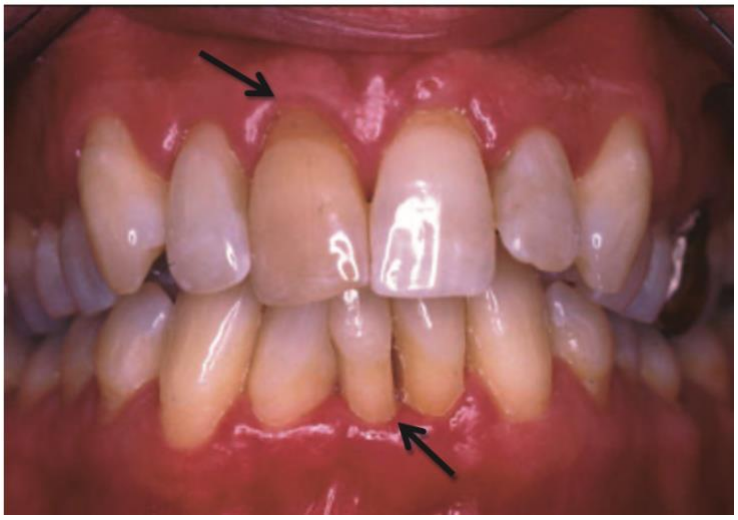


Contreras A, Botero JE, Slots J. Biology and pathogenesis of cytomegalovirus in periodontal disease

3) HIV

There is a direct association between periodontal disease and systemic conditions (cardiovascular diseases, diabetes, renal disorders…). Oral manifestations are the first clinical observations of the viral infection. HIV complemented with hypertension and renal disorders intensify the severity of periodontal bone loss: Oral fungi mainly from oral mucosa contribution in severity of periodontal inflammation in HIV positive patients, but it is still unclear. (12)

HIV has some predisposition for chronic periodontitis & associated with Linear Gingival Erythema (LGE), necrotizing gingivitis (NG), necrotizing periodontitis (NP). (10)



Asia S.
Periodontal disease in HIV/AIDS

This picture (figure 3) shows the typical clinical presentation in a HIV patient with chronic periodontitis, with big gingival recession (arrows) and attachment loss. Actually, it is related to the decrease of the amount of CD4. It is explained mainly by the development of fungal, bacterial and viral infections and sometimes alteration in the harmful inflammatory response. The differences in periodontal parameters between patients following antiretroviral treatment and the negative HIV patients is still controversial. (13)

4) HPV

HPV is present in periodontal pocket and gingival sulcus & detected in patient with chronic periodontitis & patient healthy gingiva. A synergy between HPV infection – chronic periodontitis can be highlighted. (14) Indeed, the changes, generated by periodontal pathogens from inflammatory responses, form periodontal pockets with the harm of alveolar bone and finally the loss of the tooth. (15)

5) EBV

It affects around 90% of humans, through oral secretion or blood. Its main site of persistence of EBV in the body is resting memory B cells, resulting in infectious mononucleosis. It is associated with other diseases such as cancers and auto-immune diseases, with Oral hairy leukoplakia being the main EBV associated lesion.
Regarding the location, there is a higher evidence of EBV in shallow pocket of patients with low control of the glycemia.(7)

Significative relationship with chronic periodontitis exists, and correlate with the pocket depth and its predominance in gingival crevicular fluid and saliva.(16)

Comparing CMV and EBV, it seems to have a special role in the etiopathogenesis od the severe form of periodontal disease. The genome of these virus is usually found in big proportion in progressive periodontitis in adults, both general and localized, acute ulcerative necrotizing gingivitis, periodontal abscesses.(8)
As last, we can't leave out the global impact of the current virus: the Covid-19 has given a new boost with virus research.

Objectives

Primary objective:

The primary objective of this study is to review how virus can be part of periodontal etiopathogenesis.

Secondary objectives:

1) Know if it exists scientific evidence between virus and the types of virus in the periodontal areas.

2) Approach on the relation between the oral cavity and Covid 19.

Material and Method

After the selection of the thesis subject, investigation based on scientific information and evidence in articles is the next step.

The sources used for it were pubmed.gov, NCBI, Medline complete EBSCO Health, Dialnet Plus.

The research has been done according to key words: Virus, Virus periodontal, virus periodontitis, periodontal diseases, virus transmission. The relation between periodontal diseases and Covid-19 has been studied.

It is limited on full text articles and the date of publication between 2000 and 2020.

At first, 600-650 articles were found. 350-400 articles were then selected.

According to the type of articles, all those that were not focusing on the subject were eliminated.

Then after a first reading of these lasts, the final list of articles has been established according to the following inclusion criteria article's name, origin, parameters, results, conclusion and specific observations parts.

This procedure has been followed all along the reading in order to get a structured work.

Eligbility criteria

Inclusion criteria:

- Publications in English and in Spanish were included.
- Publications that reported on the role of several virus and its mechanism in the process of periodontal diseases were included.
- Publications that reported on the origin and evolution of oral viruses were included.

Exclusion criteria:

- Publications that exclusively reported on bacteria were excluded.
- Publications that reported on immunity, and chemistry mainly were excluded.
- Publications that reported on animals were excluded.
- Publications that reported on a unique population were excluded.

Results

Authors/year of publication	Origin	Parameters	Results
Jorgen Slots, 2010 John Wiley & Sons A/S	Periodontology 2000		- Study from Turkey of young military with generalized periodontitis: Detection of HSV type 1, EBV and CMV in 73-78% of advanced lesions samples. Absence virus in subgingival sites in healthy periodontium patients. - Hopi American Indian population of 75 adolescents: 1 of them has generalized aggressive periodontitis with a periodontal dual infection, EBV type 1 and CMV. - 16 subjects from Greece with early periodontitis: 2 disease-active sites with average pocket depth = 6,8mm 2 disease-stable sites with average pocket depth = 5,6mm - Marked association of EBV, CMV and EBV-CMV with disease-active periodontitis and with several bacteria. - Detection rate of herpesvirus in biopsies from gingiva of chronic periodontitis lesions of patients from Los Angeles. - Hochman et al. : Antibodies against EBV in 32% and against CMV in 71% of gingival crevice fluid samples from 34 study sites. IgA in gingival crevice fluid and IgG in serum samples represente the main part of antibodies against herpesvirus.
Marija Ivanovska-Stojanoska et al. 2018 sept. 25	ID Design Press, Skopje, Republic of Macedonia. Open Access Macedonian Journal of Medical Sciences. Dental science	Medical faculty of Skopje. 89 patients with chronic periodontal disease divided into 2 groups (moderate and severe periodontitis). - Clinical and laboratory	- 60,7% of patients with HSV-1 in moderate clinical stage. - 39,3% in advanced clinical stage. - in 24,7 % (22 patients of all 89 patients) with moderate and advanced PD: HSV-1 detected in supra and/or subgingival dental plaque samples. - No significant difference in frequency of detect HSV-1 between moderate and

		examinations: Removal of supragingival dental plaque samples with sterile cotton. Removal of subgingival dental plaque samples with paper absorbents. - DNA is removed and analyzed with multiplex PCR for presence of herpes viral DNA.	advanced periodontal disease patients from statistical analysis. - Statistical difference in HSV-1 positive patients with moderate disease stage between presence of virus in supragingival (100%) and subgingival (16,7%) in dental plaque samples. No significant difference in the advance disease stage, HSV-1 positive patients.
Khalid Al-Hezaimi et al. 2012	Journal of the College of Physicians and Surgeons Pakistan	Case report that exposes the big periodontal destruction in patient infected with HIV. 49 years old male reported with 10 years history of infection with HIV and 3 years history of vision loss, renal failure and hypertension.	After 1 year follow-up, we could see on radiographs an aggressive and generalized horizontal alveolar bone loss of 7-8 mm in both arches.
Luigi Nibali et al. 2009	Journal of Clinical Periodontology 2009. Periodontology unit, Eastman dental institute; Centre for virology, university College London, UK.	Case control design: - 140 participants - Inclusion criteria for periodontitis patients: at least 3 probing pockets depth (PPD) of 5mm or more and clinical attachment loss (CAL) in at least 3 different quadrants. - Inclusion criteria for control patients: absence of pockets depth (PPD) of 5mm or more and lifetime cumulative clinical attachment loss (CAL) with history of periodontitis and	20 individuals with Chronic periodontitis (CP) 16 individuals with LAgP 64 individuals with GAgP. 40 individuals classified periodontally healthy. Detection rate of viral DNA in subgingival plaque samples. Absence of HCMV DNA in individuals. Black subject positive for EBV. More EBV detected in LAgP (25%) than GAgP and CP cases. Nothing significative between cases and controls.

		periodontal treatment. - PCR analysis as chosen method to detect viral DNA.	
Sanja Matić Petrović et al. 2014	Department of periodontology and Oral medicine. Laboratory of anthropology, department of anatomy. Institute of human genetics, school of dental medicine. University of Belgrade, Serbia.	- In gingival crevicular fluid (GCF) - Prevalence of HSV-1 and periodontal destruction - Serbian population *Study*: - 67 subjects (18-76 years old). 36 with periodontitis/31 volunteers.	- No statistical differences between periodontal group (PG) and control group (HC) in the presence of HSV-1. No difference neither in mean age nor between gender. - In the PG group, significant differences depending on the presence of the virus: higher values in patients with HSV-positive in probing pocket depth and clinical attachment loss (CAL). Also, HSV-1 exists more often in deeper pockets (3/4 deepest pockets of 11 mm with HSV-1.
Patrícia Rodrigues et al. 2015	Journal of oral and maxillofacial pathology Vol 19 Issue 3 Sep-Dec 2015		- Individual lesions of AP can produce subgingival herpes viruses around 89% for EBV, 78% for CMV, 87% for HSV-1 and 64% for herpes virus type.
Adolfo Contreras, Jørgen Slots. 2000	Journal of periodontal research	8 herpesvirus species identified: - HVS type 1, 2, 3 - Varicella zoster virus (VZV) - EBV - HCMV - HHV-8	*Table 2.* Herpesviruses in gingival biopsies from periodontal health and periodontitis (91) Viruses / Periodontal health (11 subjects) / Periodontitis (14 subjects) / *p*-values (chi-square test) HSV 1 (9)[a] 8 (57) 0.04 EBV-1 3 (27) 11 (79) 0.03 EBV-2 0 (0) 7 (50) 0.02 HCMV 2 (18) 12 (86) 0.003 HHV-6 0 (0) 3 (21) 0.31 HHV-7 0 (0) 6 (43) 0.04 HHV-8 0 (0) 4 (29)[b] 0.17 [a]No. (%) virally positive samples. [b]3 patients were confirmed HIV-positive. Table 1.(17)
Antonella Rotola et al. 2008	Journal of clinical periodontology. Founded by the british, dutch, French, german, Scandinavian and swiss societies of periodontology.	37 subjects : 24 affected by periodontitis, 13 periodontally healthy. ChP (chronic periodontitis) patients: At least five sites with clinical attachment level (CAL) of 5 mm or more and eight sites with pocket probing	- EBV prevalent significantly higher in periodontal patients and areas affected than healthy control patients. - No significant correlation for HCMV and HHV-7, similar results in ChP and AgP. - When HHV-7 is detected, it persists in its latent state in most of the cases. - High tropism of HHV-7 for gingival tissues, assessed as a major reservoir for the virus. - EBV much more present in periodontitis patients (50%) than in healthy patients. (7,7%).

		depth (PPD) of 6 mm or more. AgP (aggressive periodontitis) patients: CAL of 5 mm or more in more than four teeth apart from first molars or incisors; Healthy subjects: no sites with PPD superior or egual to 4 mm or inter-dental CAL loss >/=2 mm.	

Discussion

The oral cavity is very susceptible to viral infections. Between the numerous virus well known, several of them are seen as oral disease causing primary lesions. To this is added the fact that a secondary pathological process can affect the oral cavity medium through bacterial, fungal infections due to viral immunosuppression (HIV).

In the following, the main virus involved in these mechanisms will be studied.

Herpes virus

The interaction between herpes virus, destructive inflammatory mediators and specific pathogenic bacteria leads to the development of periodontal disease. No significant difference has been found in the various statistical analysis that were carried about the frequency of detection of HSV-1 between moderate and advanced periodontal disease patients but there is a significant statistical difference found in HSV-1 positive patients with moderate disease stage between presence of virus in supragingival (100%) and subgingival (16,7%) dental plaque samples. However, a notable difference can't be found in the advance disease stage, HSV-1 positive patients.

There is a positive correlation between the presence and frequency of herpes viruses in periodontal pocket and periodontal pocket depth. (18)

The discovery of herpes virus in periodontal tissues, gingival crevicular fluid (GCF) in chronic, advanced and aggressive periodontitis and in HIV patients, Papillon-Lefèvre, Down, Kostmann helps to consider nowadays the pathogenesis of a few types of periodontitis as a "multiple step process" through complex interaction between host, bacteria, viruses and environmental factors.(9)

Periodontal diseases

As mentioned previously and confirmed in various researches, periodontitis is a multifactorial disease involving herpes virus, bacteria and host defense reactions. (19)
Also, a study shows no statistical differences between periodontal group (PG) and control group (HC) in the presence of HSV-1, and no difference neither in mean age nor between gender. In the periodontal group, significant differences subsist depending on the presence of the virus: superior values in patients with HSV-positive in probing pocket depth (PPD) and clinical attachment loss (CAL). HSV-1 exists more often in deeper pockets (3/4 deepest pockets of 11 mm with HSV-1.(9)
Indeed, among all the study, the relation between the presence of HSV-1 and pocket depth is the most relevant result: significant greater prevalence of HSV-1 in deeper pocket than in shallower ones. As well as CAL and PPD. (9)
Moreover, there is additional tissue destruction in periodontal pockets infected with herpes viruses compared to pocket areas of not infected with herpes virus. Also, a close association between active viral herpetic infection and progressive periodontal disease is pointed. (19)

HCMV and EBV

A high prevalence of HCMV and EBV has been noticed in the group of chronic periodontitis and aggressive periodontitis. (6)(16) Kubar et al commented a bigger periodontal pocket depth and attachment loos in AP areas with HCMV than areas without HCMV.(19)
CMV and EBV seems to have a special role in the etiopathogenesis of the severe form of periodontal disease. The genome of these virus is usually found in big proportion in progressive periodontitis in adults, both general and localized, acute ulcerative necrotizing

gingivitis, periodontal abscesses.(8) As concluded by a study, the reactivation of HCMV in periodontitis is associated with progressing periodontal disease. (17)

Table 2. Herpesviruses in gingival biopsies from periodontal health and periodontitis (91)

Viruses	Periodontal health (11 subjects)	Periodontitis (14 subjects)	*p*-values (chi-square test)
HSV	1 (9)[a]	8 (57)	0.04
EBV-1	3 (27)	11 (79)	0.03
EBV-2	0 (0)	7 (50)	0.02
HCMV	2 (18)	12 (86)	0.003
HHV-6	0 (0)	3 (21)	0.31
HHV-7	0 (0)	6 (43)	0.04
HHV-8	0 (0)	4 (29)[b]	0.17

[a]No. (%) virally positive samples. [b]3 patients were confirmed HIV-positive.

(17)

Also, it has been seen that EBV and HCMV are associated with apical and marginal periodontitis. HCMV was not present in the apical samples and in a really small quantity in the marginal samples. Different results according to authors: Klemenc et al. are in accordance with these results, however Slots found much higher prevalence. “EBV was detected in 45% of the lesions, being less than in some other previous studies.”(20) Periodontal area with HCMV, EBV-1 or herpes simplex virus type 1 has a predominance of Porphyromonas gingivalis and Dialister pneumosintes compared to areas without theses viruses. In fact, areas with active HCMV have more aggregatibacter actinomycetemcomitans compared to areas with latent HCMV. An hypothesis is made suggesting that active periodontal HCMV infections triggers overgrowth of subgingival Actinobacillus actinomycetemcomitans leading to periodontal deterioration. (17)

According to Saygun et al**.,** HCMV, EBV-1 and HSV-1 have a positive association with P.gingivalis, Prevotella intermedia, tannerella forsythia and campulobacter rectus but not with A. actinoycetemcomitans. (19) Herpesvirus present a high quantity of periodontopathic bacteria such as actinobacillus, actinomycetemcomitans, Porphyromonas gingivalis,

bacteriodes forsythus, Prevotella intermedia, Prevotella nigrescens and treponema denticola.(17)

Regarding EBV, in 1996 the first report about the association between EBV and chronic periodontitis (CP) turned up. A lot of controversy remains: some authors say that high prevalence of EBV DNA increases the risk of periodontal diseases. Others affirm that there is a weak to no relationship between them.(21) In reality, there are more EBV and CMV in areas of aggressive and progressive periodontitis than in chronic periodontitis. But other studies propose a similar occurrence of EBV and CMV in aggressive periodontitis.(1)

A close association between EBV and periodontitis is shown mainly in Chronic Periodontitis and Aggressive Periodontitis.(21)(16)

A study talked about the fact that periapical lesions could be defined as reservoir for EBV with a systemic spread. Fusobacterium is the most potent inducer to reactivate latent EBV and has a “pivotal role” in EBV-related tissue damage, in persistent apical periodontitis.(22)

HIV

HIV has predisposition for chronic periodontitis. It is associated with Linear Gingival Erythema (LGE), necrotizing gingivitis (NG), necrotizing periodontitis (NP), chronic periodontitis. HIV-positive patients are predisposed to chronic periodontitis with attachment loss higher than HIV-negative patient. (10)

Murray et al. affirm a higher prevalence of periodontal pathogens in sub-gingival plaques removed in HIV positive patient than negative ones. The association between increased bacterial counts and overproduction of endotoxins, leading to higher periodontal bone loss. But there is still controversy. It suggest a non unique plaque flora in the aggressive nature of

periodontal disease HIV patient.(12) In fact, bacteria predominance are Fusiform, spirochetes, borelia and candida albicans bacteria. HIV associated periodontitis, as HIV associated gingivitis, doesn't have sites of predilection and can affect any teeth groups with same frequency. In most of the cases, the periodontal destruction is localized more than generalized. Through chronic inflammation of the periodontium, there is pocket formation through a quicker attachment loss progression than gingiva destruction. It will happen in few weeks, leading to complete attachment loss though spontaneous tooth loss. Two characteristic features of rapid bone loss are soft tissue craters and interproximal necroses.(23)

Other authors*, Cross and Smith,* studied a culture with a colony lift method and DNA probes to compare plaque and found that there is a similar prevalence of periodontal pathogens from both groups HIV positive and negative patients. The only one difference is a slight significant higher proportion of P. gingivalis in HIV positive patients.So, it suggests a non unique plaque flora in the aggressive nature of periodontal disease HIV patient.

In general, HIV patients are affected by a rapidly progressive periodontal disease more than a slowly progressive one compared to HIV negative patients. The oral manifestations are the first clinical observations of the viral infection. (12)

HPV

HPV is commonly present in periodontal pocket and gingival sulcus. The fact that the periodontium is a reservoir for HPV is hypothetic. It is detected in patient with chronic periodontitis & patient healthy gingiva (periodontal pockets, gingival sulci of posterior lower teeth) and mainly found in the marginal periodontium. We can talk about a "synergy chronic periodontitis - HPV infection in patient that don't undergo head and neck squamous cell carcinoma".(14)

Also, it has been mentioned that there is positive association of HPV with periodontitis. Actually, chronic periodontitis eases the life cycle of HPV. In this study, through PCR test, a high risk HPV was present in 26% of the gingival biopsies. Through in situ hybridization, viral DNA had a coronal localization according to the junctional epithelium in the periodontal pocket.

By deduction, a positive correlation subsists between E6/E7 mRNA values and gingival index values. Basal cells seem to be the site of latent HPV. In periodontitis, the formation of periodontal pocket occurs through the rapid proliferation of the basal cells. Of the junctional epithelium. In this case, it is shown that periodontal pocket epithelium is a favorable place for HPV to replication.(24)

As previously mentioned, periodontopathic synergy virus-bacteria is demonstrated in a studied critical review.(7)(25) The pathogenesis of periodontal diseases can't not be perfectly explained by bacterial etiology itself. Nowadays, we consider the pathogenesis of some types of periodontitis as a "multiple step process" implying a complex interaction between host, bacteria, viruses and environmental factors.(9)

A link herpesvirus-bacteria exists as co-infection and close association, even a bidirectional interaction. Herpesviruses don't work alone but in cooperation with other specific bacteria as periodontopathic agents in periodontal tissues destruction. (1)

There is a virus-bacterium-host interaction: virus-infected periodontitis lesions and periodontopathic bacteria (Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Dialister pneumosintes, Prevotella intermedia, Prevotella nigrescens, Treponema denticola). (4)

Through a study done in Macedonia, the etiopathogenesis of periodontal disease is explained by association of Herpes virus and specific pathogenic bacteria. Indeed, the development of periodontal disease depends on interaction between herpes virus, specific pathogenic bacteria and destructive inflammatory mediators.(18)

The proposed mechanism of periodontal pathogenesis is defined by Slot in 2005 as the capacity of herpes virus to provoke immunosuppression and eventually a direct cytopathic effect on fibroblasts, keratinocytes inflammatory cells. Despite the limitations of ethnicity population and small sample size, we can conclude that there is a very low prevalence of subgingival herpes virus in periodontal lesions. Only Localized Aggressive Periodontitis cases shown moderate prevalence of EBV but still not significant from the control patients.(6)

In “Avances en Periodoncia” article, in the etiology of the periodontitis, bacteria are central and essential but not unique. We consider periodontal disease as a multifactorial concept as its development and progression will depend on the age, the origin, the socio-economic situation, systemic conditions, habits.(8) In reality, we can’t generalize that specific infectious agents are the only agents involved in the periodontitis process. It consists generally in small groups of pathogens as actors of periodontal diseases. AP is not only provoked by anaerobic gram negative bacteria but by a various microbiota. (19)

Through all the studies and articles reading, limitations and controversy are recurrent. For example, there are still doubts on the role of viruses with periodontal disease. (10) The etiopathogenesis of periodontal disease not clear. The development of periodontitis is initiated.(9) According to the postulates of Hill, there is a possible association between virus and periodontal diseases. But the fact that the periodontal disease is multifactorial with long

period of latency, not reproducible experimentally, makes it difficult to establish a causal relation. (8)

Also, there is a persistent lack of information about herpes virus and its role in aggressive periodontitis. It is still not understood why patient with periodontopathic bacteria in saliva present periodontitis in few localized teeth.(19)

Conclusion

Primary objectives: The spread of infection and the viral pathogenesis require to understand the detailed process of the cellular machinery of the host.(5) Generally, the immune system defenses are weaken, the virus hinders the antibacterial immune process and it leads to the growth of the periodontopathic microbiota. It's an interactive procedure between virus and bacteria in the building process of periodontal diseases. Also, virus don't work alone but usually in cooperation with other specific bacteria as periodontopathic agents in periodontal tissues destruction.(1) Indeed, virus infection impair periodontal defense capacities leading to subgingival overgrowth of periodontopathic bacteria.(4) Inflammation and bone resorption are generated due to the implication of cytokines in the pathogenesis of periodontitis. Dental plaque is assessed as a big element in the pathogenesis of periodontitis. But viral disease of the periodontium could also be placed under non-plaque induced gingival lesions (herpetic gingivostomatitis, varicella zoster…).(26)

It has been properly demonstrated that there is a periodontopathic synergy between virus and bacteria.(7)

But, still uncertainties on the role of viruses with periodontal disease.(10) The mechanism is not clear yet and several controversy subsist. (4) Virus are since recently involved in the pathogenesis of periodontitis.(6)

Secondary objectives:

1) Periodontitis has a not clear origin: either genetic or environmental in predisposed patients. (1) Over a million copies of HSV genomes could be involved in only one single active periodontal destruction such as periodontal pocket. In the case of HIV at a systemic level, it

is important to monitor HIV infected patients in order to minimize local periodontal inflammation and destruction.(12)

According to the postulates of Hill, there is a possible association between virus and periodontal diseases. But the fact that the periodontal disease is multifactorial with long period of latency, not reproducible experimentally, makes it difficult to establish a causal relation.

We must not lose sight of the fact that nowadays, it is more and more evident that several viruses replicate in the human body in an asymptomatic way.(20)

2) Last but not least, evidence shows the collect of SARS-CoV-2 from saliva but it's not the only exudate in the oral cavity: in fact, the gingival crevicular fluid is of importance in the study of the condition of the periodontium (Taylor et al. 2016). The GCF is used as a mean of detection of virus such as herpes simplex virus, HCMV in a sampling. Briefly, in addition to be a mode of infection, the GCF has efficiently proven to be used as a diagnostic tool in the pathophysiology of COVID-19.(27)(28)

From this stems the significant role of the oral cavity and its mucosae in the process of infection of COVID-19, considered as the entrance portal in the body and virus reservoir.(29)

Responsibility

The current pandemic situation has given rise to a lot of doubts in the society. This literature review tends to present an interesting study of the different viruses including the Covid-1 and its relation with periodontal area. Indeed, herpesviruses are the widely represented and known viruses by the general population. It is considered important its examination with the oral microbiota.

Nowadays, with new technologies and science advances, the diagnosis and the treatment of periodontal diseases is easier.

Also, patients need to be aware of the existing association with common viruses. To this is added the new in coming of the Covid-19: In fact, it has been studied the different characteristics and its impact on the oral flora.

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Annexes:

Periodontology 2000, Vol. 53, 2010, 89–110
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PERIODONTOLOGY 2000

Periodontology 2000

Human viruses in periodontitis

JØRGEN SLOTS

Periodontitis affects the majority of adults worldwide (4), but relatively few patients receive adequate treatment for the disease (9). Conventional periodontal therapy includes a stabilization phase and a maintenance phase. Stabilization of the disease is accomplished by periodontal mechanical depuration and the removal of calculus and other biofilm-retentive factors, and may involve adjunctive antimicrobial medication and/or surgery. The long-term goals in the maintenance stage are to have patients exercise proper plaque control and to commit to professional antimicrobial treatment in order to minimize the likelihood of a clinical relapse.

Current periodontal therapy is successful in combating initial and moderate types of periodontitis, but may show limited efficacy in resolving late-stage disease. Optimal periodontal care is often impeded by the lack of patient cooperation and by affordability issues. Periodontal treatment can entail substantial costs attributed to direct healthcare expenses and to loss of income during the time of professional therapy. A greater understanding of the etiopathogeny of periodontal disease seems to be a prerequisite for the development of preventive and therapeutic strategies that are more efficacious and less burdensome for patients.

The task of determining the periodontopathic importance of suspected disease determinants is hampered by difficulty in identifying the initial stage of periodontitis and in distinguishing between progressive and stable phases of the disease. Differences in case definitions and diagnostic methods also complicate the interpretation of epidemiological findings in periodontal research. Periodontitis typically occurs in otherwise healthy individuals and is statistically associated with various environmental and demographic factors (3). The disease can also be linked to rare immunogenetic defects or be part of systemic diseases that primarily affect nonoral tissues (75). It is not clear if some of the proposed risk factors for periodontal disease reflect true genetic or immunological variations, or merely poor health-seeking behavior related to socioeconomic factors, lifestyles or cultural differences.

Microbiological culture and culture-independent molecular studies have identified more than 1,200 bacterial species (140) and 19,000 phylotypes (91) in the oral cavity. At least 400 bacterial species inhabit subgingival sites (141), but despite the long list of different bacteria in periodontitis, fewer than 20 species are considered to be major periodontal pathogens (175, 185). Healthy periodontal sites harbor a scant microbiota of predominantly gram-positive facultative bacteria, whereas periodontitis lesions contain a large variety of gram-negative anaerobic species (171). The shift in the periodontal microbiota with disease development is the result of a multifaceted interaction of microbial-specific traits, host immune responses and ecosystem-based factors. It is not known why fastidious gram-negative anaerobic bacteria outcompete common oral gram-positive bacteria, and why relatively few suspected periodontopathogens are surging in numbers in periodontitis sites.

Periodontopathogenicity is assessed primarily on the basis of an elevated occurrence of a given bacterial species in advanced periodontitis lesions. However, many anaerobic bacteria benefit from proteinaceous components that are present in the gingival crevice fluid and may merely be secondary invaders of periodontitis sites. Also, the cross-sectional design of most bacteria–periodontitis association studies prevents the pathogenetic importance of specific microorganisms from being firmly established. An important exception to this is *Aggregatibacter actinomycetemcomitans* in localized aggressive (juvenile) periodontitis (184). As expected for a true pathogen, the subgingival counts of *A. actinomycetemcomitans* have, in longitudinal studies, shown a dramatic increase immediately prior to clinical attachment loss and a marked decrease at the time of disease remission (16, 64).

Theories proposed so far to explain the etiopathogeny of periodontitis have not been able to

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ANNALS OF THE NEW YORK ACADEMY OF SCIENCES
Special Issue: *Genetic Novelty and Genomic Variation by RNA Networks and Viruses*
PERSPECTIVE

What viruses tell us about evolution and immunity: beyond Darwin?

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We describe mechanisms of genetic innovation mediated by viruses and related elements that, during evolution, caused major genetic changes beyond what was anticipated by Charles Darwin. Viruses and related elements introduced genetic information and have shaped the genomes and immune systems of all cellular life forms. None of these mechanisms contradict Darwin's theory of evolution but extend it by means of sequence information that has recently become available. Not only do small increments of genetic information contribute to evolution, but also do major events such as infection by viruses or bacteria, which can supply new genetic information to a host by horizontal gene transfer. Thereby, viruses and virus-like elements act as major drivers of evolution.

Keywords: Darwin; viruses; evolution; horizontal gene transfer

Beyond Darwin?

Charles Darwin revolutionized our understanding of the origin and evolution of species. The central tenets of his theory of evolution state that hereditary variation occurs slowly due to the gradual accumulation of random small modifications that are subject to natural selection. The discovery of DNA as a carrier of the hereditary information then allowed linking inherited traits to mutations in DNA. Today, we also know that RNA, with its high plasticity due to the relatively high infidelity of RNA polymerases, can exert strong evolutionary influences. New technologies for high-throughput genome sequencing have recently led to the discovery of multiple novel forms of mutations and genetic alterations.

Fundamentally new insights into these influences have come from viruses and microorganisms, infectious agents that can supply genetic material into recipient cells by horizontal gene transfer (HGT). For instance, up to two-thirds of the human genome sequence is derived from viruses and transposable elements,[1,2] and a smaller proportion of DNA sequence originates from bacteria and other microorganisms.[3–5] In contrast to point mutations, small insertions, or small deletions, which have conventionally been regarded as the major driving forces of evolution, the supply of new genes by HGT can cause dramatic changes to an organism almost instantaneously. In addition to HGT, major genetic changes are induced by crossover and recombination events, (retro)transposition activity, transformation, and conjugation;[3–6] well-studied examples include uptake of plasmids that confer antibiotic resistance to a bacterial cell.[7] Furthermore, RNA agents, including RNA viruses and viroids, typically lack proofreading mechanisms during their replication and thus can accumulate mutations more rapidly than replicating DNAs.[8,9] Retroviruses, with their high genomic plasticity and life cycle that includes obligatory integration into the host genome, are among the major drivers of evolution by, among other things, providing novel genes and regulatory elements.[10–13] Retroviruses have accumulated in large numbers into eukaryotic genomes, mediate HGT, transduce cellular genes including oncogenes, and contribute to cancer.[1,2,10]

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ORIGINAL ARTICLE

Transboundary and Emerging Diseases WILEY

Rapid identification of human-infecting viruses

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Abstract

Viruses have caused much mortality and morbidity to humans and pose a serious threat to global public health. The virome with the potential of human infection is still far from complete. Novel viruses have been discovered at an unprecedented pace as the rapid development of viral metagenomics. However, there is still a lack of methodology for rapidly identifying novel viruses with the potential of human infection. This study built several machine learning models to discriminate human-infecting viruses from other viruses based on the frequency of *k*-mers in the viral genomic sequences. The *k*-nearest neighbor (KNN) model can predict the human-infecting viruses with an accuracy of over 90%. The performance of this KNN model built on the short contigs (≥1 kb) is comparable to those built on the viral genomes. We used a reported human blood virome to further validate this KNN model with an accuracy of over 80% based on very short raw reads (150 bp). Our work demonstrates a conceptual and generic protocol for the discovery of novel human-infecting viruses in viral metagenomics studies.

KEYWORDS
human-infecting virus, machine learning, viral metagenomics, virome

1 | INTRODUCTION

Viruses are the most abundant biological entities on Earth and exist in all habitats of the world (Paez-Espino et al., 2016). They can infect all kinds of organisms in a range from the bacteria to animals, including humans. Humans are constantly exposed to a vast diversity of viruses, and over two-thirds of human pathogens belong to viruses (Woolhouse & Gaunt, 2007). The viruses have caused colossal mortality and morbidity to the human society in history, such as the devastating smallpox and Spanish flu outbreaks (Johnson & Mueller, 2002; Riedel, 2005). Despite the continuous progress in the prevention and control of viral disease, recent serial outbreaks caused by the Middle East respiratory syndrome coronaviruses (Breban, Riou, & Fontanet, 2013), avian influenza H7N9 viruses (Gao et al., 2013), Ebola viruses (Maganga et al., 2014) and Zika viruses (Mlakar et al., 2016) indicate that viruses still pose a severe threat to global public health.

To this date, the virome with the potential for human infection is still far from complete. Generally, a new pathogen would not be identified until it caused epidemics or pandemics. Many viruses that may have been introduced into human populations remain undiscovered (Rosenberg, 2015). Traditional diagnostic methods such as polymerase chain reaction, immunological assays and pan-viral microarrays are inadequate for the quick identification of novel human-infecting viruses (Corman et al., 2012; Wootton et

Zheng Zhang and Zena Cai contributed equally to this work.

VIRUSES IN PERIODONTAL DISEASES

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INTRODUCTION

Viruses are one of the smallest forms of microorganism (10–100 nm) which can only multiply inside living cells.[2] consists of the nucleocapsid, which may be "naked," or "enveloped" within a lipoprotein sheath derived from the host cell membrane. Periodontal diseases are those diseases that affect one or more of the periodontal tissues: gingiva, periodontal ligament, cementum and alveolar bone.[3] The most recent classification is based on the 1999 International Workshop for the Classification of the Periodontal Diseases organized by the American Academy of Periodontology.[3,4] Viral diseases of the periodontium are placed under non-plaque induced gingival lesions and they include herpetic gingivostomatitis, varicella zoster and others. Many bacterial infections in humans occur as super infections of viral diseases. A well known example of this bacterial complication is influenza.[5] Dental plaque is important in the pathogenesis of periodontitis. Experimental studies have shown that, oncean individual abstains from mechanical tooth-cleaning micro organisms start to colonize the tooth surfaces,clinical signs of gingivitis appear within a few days.[6] The benefit of adjunctive antibiotic therapy to mechanical debridement supports the argument that bacteria play a major etiological role in human periodontal diseas.[7]

Classification: Viruses are classified according to nucleic acid composition:

Deoxyribonucleic acid (DNA) or ribonucleic acid (RNA).

Abstract

Periodontal diseases are infectious diseases, but the specific mechanism by which the tooth-supportive tissue is destroyed is not clearly understood.. Viral infection impairs periodontal defenses, thereby permitting subgingival overgrowth of periodontopathic bacteria. Gingival tissue plays a role in the maintenance of viral load in vivo and that the shedding of viruses from periodontal sites during reactivation plays a role in virus transmission. Evidence suggests that virus-infected periodontitis lesions harbor elevated levels of periodontopathic bacteria, including Actinobacillus actinomycetemcomitans, Porphyromonas gingivalis, Dialister pneumosintes, Prevotella intermedia, Prevotella nigrescens, and Treponema denticola Clearer understanding of roles of viruses in periodontal diseases will facilitate periodontal disease prevention and treatment.

Objective : The purpose of this review is to give an overview of the viruses involved in periodontal diseases, and to evaluate the evidence that viral infection plays a role in the development of periodontal diseases.

KEYWORDS: Virus, Periodontitis,Virus-Bacterium-Host interaction

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REVIEW ARTICLE

Virus entry paradigms

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Abstract Viruses, despite being relatively simple in structure and composition, have evolved to exploit complex cellular processes for their replication in the host cell. After binding to their specific receptor on the cell surface, viruses (or viral genomes) have to enter cells to initiate a productive infection. Though the entry processes of many enveloped viruses is well understood, that of most non-enveloped viruses still remains unresolved. Recent studies have shown that compared to direct fusion at the plasma membrane, endocytosis is more often the preferred means of entry into the target cell. Receptor-mediated endocytic pathways such as the dynamin-dependent clathrin and caveolar pathways are well characterized as viral entry portals. However, many viruses are able to utilize multiple uptake pathways. Fluid phase uptake, though relatively non-specific in terms of its cargo, potentially aids viral infection by its ability to intersect with the endocytic pathway. In fact, many viruses despite using specialized pathways for entry are still able to generate productive infection via fluid phase uptake. Macropinocytosis, a major fluid uptake pathway found in epithelial cells and fibroblasts, is stimulated by growth factor receptors. Many viruses can induce these signaling cascades in cells leading to macropinocytosis. Though endocytic trafficking is utilized by both enveloped and non-enveloped viruses, key differences lie in the way membranes are traversed to deposit the viral genome at its site of replication. This review will discuss recent developments in the rapidly evolving field of viral entry.

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Keywords Enveloped virus · Non-enveloped virus · Endocytosis · Membrane fusion · Signaling

Introduction

Viruses, like all obligate intracellular pathogens, have to find the means to cross cellular membranes. This is the key to initiating their infectious cycle, and involves a number of discrete steps like receptor binding and entry, capsid destabilization and genome uncoating, culminating in the release of viral nucleic acids at their site of replication. Many of these changes result from conformational alterations in metastable viral structures. Virus binding to and/or cross-linking their specific receptors can also lead to activation of downstream signaling events (Greber 2002). These signals often induce changes that promote entry, prepare the cell for invasion and neutralize host defences. In animal cells, enveloped viruses achieve entry in two principal ways: (1) by direct fusion with the plasma membrane, or (2) by an internalization process into endosomes. For viruses using the first strategy, fusion between the viral and cellular membranes occurs after receptor docking and before the virus core penetrates the cell. Recent developments in membrane trafficking have demonstrated the existence of multiple endocytic pathways at the plasma membrane (Marsh and Helenius 2006). Indeed, most viruses prefer to enter cells via endocytosis since the endocytic network confers an additional advantage of specific localization within the cell for a successful infection. In the case of endocytic entry, the virus must penetrate or fuse with the endosomal membrane to be released into the cytoplasm. Studies indicate that endocytosis serves as an entry portal for both enveloped and non-enveloped viruses. While there have been many advances in

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Journal of Clinical Periodontology

Low prevalence of subgingival viruses in periodontitis patients

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Nibali L, Atkinson C, Griffiths P, Darbar U, Rakmanee T, Suvan J, Donos N. Low prevalence of subgingival viruses in periodontitis patients. J Clin Periodontol 2009; 36: 928–932. doi: 10.1111/j.1600-051X.2009.01476.x.

Abstract

Background: Viruses such as Human Cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) have been proposed to be periodontal pathogens. The aim of this study was to analyse the presence of herpesvirus DNA in subgingival plaque samples of patients with different forms of periodontitis and in healthy periodontia.

Materials and Methods: A total of 140 ethnically mixed (prevalently Caucasian) subjects took part in the study. Sixteen were affected by localized aggressive periodontitis (LAgP), 64 by generalized aggressive periodontitis (GAgP), 20 by chronic periodontitis (CP) and 40 were periodontally healthy. Polymerase chain reaction (PCR) analyses were performed to detect HCMV and EBV. Sera were tested for anti-HCMV and EBV IgG antibodies. PCRs for herpes simplex (HSV) and varicella zoster virus (VZV) were performed in subgingival samples from a subset of 20 AgP subjects.

Results: HCMV DNA was not detected in any plaque samples. EBV DNA was detected in four LAgP (25%), two GAgP (3%) subjects and four healthy individuals (10%). HSV DNA and VZV DNA were not detected in the subset of studied individuals.

Conclusions: This study challenges the previously reported high prevalence of herpesvirus DNA in subgingival samples from periodontitis patients and so questions whether they act as pathogens in such patients.

Key words: aggressive; herpes; pathogenesis; periodontitis; virus

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Growing evidence suggests that certain viruses may play a role in the pathogenesis of periodontitis. In particular, DNA from herpesviruses such as human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) has been detected in high percentages of subgingival plaque samples from periodontitis patients. In contrast, very low prevalence of such viruses has been detected in periodontally healthy individuals (Contreras & Slots 1996, Yapar et al. 2003).

Conflict of interest and source of funding statement

This work was undertaken at UCLH/UCL who received a proportion of funding from the Department of Health's NIHR Biomedical Research Centres funding scheme. We declare we have no conflict of interest.

Furthermore, herpesviruses have been associated with severity and activity of periodontitis and with presence of periodontopathogenic bacteria (Michalowicz et al. 2000, Kamma & Slots 2003). A recent review suggested that viruses may directly induce immunosuppression and may have direct cytopathic effect on fibroblasts, keratinocytes and inflammatory cells (Slots 2005). However, large studies confirming the association between periodontitis and presence of subgingival viruses are still lacking. The aim of this study was to analyse the presence of herpesviruses in subgingival pockets and the presence of immunoglobulin G (IgG) against the same viruses in serum samples in a large prevalently Caucasian population of periodontitis and in healthy individuals.

Materials and Methods

Study population

The study had a case–control design, with a total of 140 participants. A 100 cases were selected among patients referred to the Eastman Dental Hospital, University College London by general dental practitioners. Forty unmatched healthy controls were recruited among patients referred to other Departments of the Hospital. All of the patients gave written informed consent and the study had been reviewed and approved by the Joint UCL/UCLH Committees on the Ethics of Human Research.

All participants in the study had no signs or symptoms of systemic infection or disease as assessed by the examining clinician and had not taken any systemic antimicrobials in the last 3 months.

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REVIEW ARTICLE

Periodontics

Viruses: are they really culprits for periodontal disease? A critical review

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Keywords
etiology, herpes virus, periodontal disease, periodontitis, virus.

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Abstract

Periodontal diseases are multifactorial, and many etiological agents are suggested to play a role in their etiopathogenesis. Various risk factors are also suggested to influence the progression of periodontal disease. Until recently, specific bacteria were considered the major pathogens for the disease. However, the occurrence of periodontal disease in some patient groups is still poorly understood, and the role of other initiating agents is being investigated. Evidence strongly suggests the presence of many strains of viruses in the periodontal environment, and possible mechanisms have also been suggested. Periodontal disease as a risk factor for other systemic diseases can also be better explained based on this viral etiology. In this review, we critically analyze the role of viruses in different periodontal diseases, and provide a categorical description of the underlying mechanisms. Clinical implications and future directions are also discussed. Evidence of a causal role of herpes viruses in periodontitis might revolutionize existing strategies to diagnose, prevent, and treat the disease.

Introduction

Periodontitis is a common chronic oral disease that can occur in otherwise healthy individuals. There is a plethora of information in the field of periodontology of the events before and during this disease process. Different types of bacteria were implicated in its pathogenesis. Microbiological culture and culture-independent molecular studies have identified more than 1200 bacterial species[1] and 19 000 phylotypes[2] in the oral cavity. At least 400 bacterial species inhabit subgingival sites,[3] but despite the long list of different bacteria in periodontitis, fewer than 20 species are considered to be major periodontal pathogens.[4,5]

Periodontitis is site specific, although periodontopathic bacteria are abundant in saliva. The progressive course of periodontitis typically includes prolonged periods of disease remission, interrupted by occasional episodes of clinical relapse, the underlying biological basis of which is not clearly understood. To explain this phenomenon, environmental, genetic, demographic, and host defense factors were introduced. The virulence of infecting agents was also suggested as a major determinant in the onset and severity of periodontitis, as in any other human disease. With this background, the importance of viruses in periodontal etiopathogenesis has emerged as a major research area in recent years.

Since the mid 1990s, herpes viruses have emerged as putative pathogens in various periodontal diseases.[6] At present, the evidence is so strong that it is reasonable to believe that viruses do play a real role in periodontal etiopathogenesis. Total viral copy count detected in advanced periodontitis sites might even approach the total bacterial count in some cases.[7] Evidence of a causal role of herpes viruses in periodontitis might revolutionize existing strategies to diagnose, prevent, and treat the disease. The aim of the present review is to provide a critical evaluation of the role of viruses in periodontal etiopathogenesis and their future clinical implications.

Viruses implicated in periodontal disease

Although more than 30 000 pathogenic viruses are identified, fewer than 40 viral families and genera have been

Papel etiológico de los virus en la enfermedad periodontal

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Echeverría A, Vignoletti F, Fabrizi S, Matesanz P. *Papel etiológico de los virus en la enfermedad periodontal* Av Periodon Implantol. 2007; 19, 2: 91-99.

RESUMEN

El objetivo de esta revisión es presentar la evidencia disponible que relaciona la infección por virus con el desarrollo de periodontitis. Esta relación se ha visto con los virus de la familia herpes, sobretodo el citomegalovirus humano (CMV) y el virus Epstein-Barr (VEB), así como con el virus de la inmunodeficiencia humana (HIV).

Las infecciones por herpesvirus generalmente sucede en dos fases, durante la primoinfección la clínica suele ser leve o asintomática y a esta le sigue una fase asintomática en la que el virus se encuentra en estado de latencia. Dicho estado se verá interrumpido esporádicamente por periodos de activación en los que se produce una replicación viral y posiblemente se dé una manifestación de la enfermedad que explicaría, en parte, el progreso en episodios de la enfermedad periodontal . De hecho, algunas de las causas que llevan a la reactivación del virus también se consideran factores de riesgo de la enfermedad periodontal y podrían relacionar a ambas patologías.

PALABRAS CLAVE

Herpesvirus, citomegalovirus humano, virus Epstein-Barr, virus herpes simple, enfermedad periodontal, patogénesis

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INTRODUCCIÓN

La periodontitis es una enfermedad infecciosa en cuya etiología las bacterias tienen un papel esencial pero no único. Son numerosos los estudios que han demostrado una relación causal entre el acúmulo de placa y el desarrollo de gingivitis o inflamación gingival. Sin embargo, a pesar de la evidencia de relación causal entre bacterias y enfermedad periodontal, existe una gran diversidad en la expresión de esta patología. En función de la edad, la raza, la situación socio-económica, las condiciones sistémicas o los hábitos del individuo, el desarrollo y progreso de la enfermedad periodontal serán muy diferentes, por lo que se con-

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Detection of Herpes Simplex Virus Type 1 in Gingival Crevicular Fluid of Gingival Sulcus/Periodontal Pocket Using Polymerase Chain Reaction

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SUMMARY

Introduction Pathogenesis and some characteristics of periodontitis cannot be fully explained by bacterial etiology alone. Herpes viruses may bridge the gap between clinical characteristics and molecular understanding of periodontal destruction.

Objective The aim of this study was to investigate the prevalence of herpes simplex virus type 1 (HSV-1) in gingival crevicular fluid (GCF) of healthy and damaged periodontium in Serbian population and to explore potential correlation between the presence of this virus and the level of periodontal destruction.

Methods Samples were collected from gingival sulcus/periodontal pockets by sterile paper points and the presence of viral DNA in gingival crevicular fluid was assessed by PCR.

Results There was no statistically significant difference in HSV-1 in presence between periodontitis patients (PG=38.9%) and healthy controls (HC=32.3%), (Chi-square test, with Yates' correction p=0.7574). However, HSV-1 positive patients showed significantly higher values of parameters of periodontal destruction (PPD=7.11±2.52, CAL=5.46±2.34) than periodontitis patients without HSV-1 in gingival crevicular fluid (PPD=4.70±1.79, CAL=3.39±2.65) (p values respectively, p=0.002 and p=0.023, Independent Samples T-Test). HSV-1 occurred more often in deeper (PPD≥6 mm) (69.2%) than in shallow pockets (3 mm<PPD<6 mm) (18.2%) (Chi-square test, with Yates' correction, p=0.008). Plaque index was lower in the HSV-1 positive group (0.84±0.69 vs. 1.43±0.76, p=0.023, Independent Samples T-Test).

Conclusion This study demonstrated that the presence of HSV-1 in the gingival crevicular fluid coincides with a higher degree of tissue destruction in patients with periodontitis.

Keywords: periodontitis; herpes simplex; gingival crevicular fluid; periodontal pocket

INTRODUCTION

Plaque-associated periodontal diseases are chronic infections caused by a mixed microbial flora, resulting in an inflammatory process that leads to periodontal attachment loss and ultimately tooth loss [1]. Although bacteria of dental biofilm are known to be the most important etiological factor for periodontal disease, a susceptible host is also needed. Immune-inflammatory reaction that develops in periodontal tissues in response to chronic bacterial presence results in the destruction of structural components of the periodontium [2].

Bacterial etiology has not been able to explain rapid periodontal tissue breakdown in cases with minimal plaque, or low levels of common risk factors [3]. Other aspects of periodontitis that cannot be fully explained by bacterial etiology are disease remission and reactivation [4], periodontitis site specificity [5], progression of periodontal destruction in some patients and not in others [6], evolution of gingivitis to periodontitis, or stable to disease-active periodontitis [7].

Herpes viruses and their biology may provide some answers for better understanding of mechanisms involved in the degradation of periodontal tissues.

Herpes viruses have been found in periodontal tissues and in gingival crevicular fluid in chronic [8], advanced [9] and aggressive [10] periodontitis as well as in the periodontium of HIV patients [11] and patients with the following syndromes: Papillon-Lefévre [12], Down [13] and Kostmann [14].

Currently, it is believed that the pathogenesis of some types of periodontitis is a multistep process, involving a complex interaction between the host, bacteria, viruses, and a variety of environmental factors.

OBJECTIVE

The aim of this study was to investigate the prevalence of HSV-1 in gingival crevicular fluid of healthy and damaged periodontium in Serbian population and to explore whether there is a correlation between the presence of this virus and the level of periodontal destruction.

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REVIEW ARTICLE

Viruses in periodontal disease – a review

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The purpose of this review was to evaluate the evidence supporting the hypothesis that viral infection plays a role in the development of periodontitis. An involvement in periodontal diseases has been suspected specifically for human immunodeficiency virus (HIV) and herpes viruses. An association has been demonstrated between HIV infection and some distinct forms of periodontal infection, i.e. necrotizing lesions. Furthermore, reports of increased prevalence and severity of chronic periodontitis in HIV-positive subjects suggests that HIV infection predispose to chronic periodontitis. Several studies, most of them from the same research group, have demonstrated an association of herpesviruses with periodontal disease. Viral DNA have been detected in gingival tissue, gingival cervicular fluid (GCF) and subgingival plaque from periodontaly diseased sites. In addition markers of herpesviral activation have been demonstrated in the GCF from periodontal lesions. Active human cytomegalovirus (HCMV) replication in periodontal sites may suggest that HCMV re-activation triggers periodontal disease activity. Concerns regarding sampling, methods and interpretation cast doubts on the role of viruses as causes of periodontal disease.
Oral Diseases (2005) **11**, 219–229

Keywords: human immunodeficiency virus; cytomegalovirus; Epstein–Barr virus; herpes simplex virus; periodontitis/pathogenesis

Introduction

Many bacterial infections in humans occur as superinfections of viral diseases. A well known example is the bacterial complication in influenza outbreaks: most deaths in influenza epidemics occur in elderly people and are frequently attributed to a secondary bacterial pneumonia mainly due to *Staphylococcus aureus*, *Streptococcus pneumoniae* or *Haemophilus influenzae* (Cate, 1998; Sethi, 2002). This example could be applied to other situation of viral-bacterial interactions, for example in the oral cavity. Recently, it was suggested that certain viruses might also influence the development and severity of periodontal disease.

It is generally believed that both gingivitis and periodontitis are caused by bacteria colonizing the tooth surfaces, and that the major mechanisms of periodontal destruction are initiated by bacteria. This view is based on a large number of studies essentially demonstrating an association between bacterial plaque and clinical signs of gingivitis and periodontitis. Cross-sectional studies of human populations have shown a positive correlation between the amount of plaque and the severity of gingivitis (O'Leary and Prignace, 1962) as well as bone loss (Schei *et al*, 1959). In addition, experimental short-term studies have shown that, once an individual abstains from mechanical tooth-cleaning and microorganisms start to colonize the tooth surfaces, clinical signs of gingivitis appear within a few days (Löe *et al*, 1965). The inflammatory alterations are resolved or reversed when the bacterial deposits are again removed from the tooth surfaces. Other studies have indicated that antiseptic agents such as chlorhexidine are able to suppress the bacterial colonization and the development of gingivitis (Löe *et al*, 1965; Corbet *et al*, 1997a,b), and that antibiotics could reduce plaque scores and improve gingival conditions in subjects with periodontal disease (Ciancio *et al*, 1980, 1982). The benefit of adjunctive antibiotic therapy to mechanical debridement procedures in controlling several forms of periodontitis further strengthens the argument for a major etiological role of bacteria in human periodontal disease (Herrera *et al*, 2002).

While the role of bacterial plaque in general seems to be evident, the following observations indicate that other functions may contribute to the development of periodontal diseases. Although all subjects with poor oral hygiene develop gingivitis, not every gingivitis lesion invariably leads to attachment loss. Despite a large variation in general levels of oral hygiene and gingivitis in different societies, and a high prevalence of potential bacterial pathogens in certain populations (Eisenmann *et al*, 1983; Dahlén *et al*, 1989; McNabb

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Biology and pathogenesis of cytomegalovirus in periodontal disease

Adolfo Contreras, Javier Enrique Botero & Jørgen Slots

Our knowledge of viral infections has increased significantly in the past couple of decades. New viruses and their pathogenicity are constantly being identified and characterized. Norovirus has joined the rotaviruses as a major pathogen of gastroenteritis, and metapneumovirus, hantavirus, niphavirus, hendravirus, Ebola virus and severe acute respiratory syndrome (SARS) coronavirus were identified after fatal respiratory outbreaks (71, 83, 85, 92, 184). Human herpesvirus species have been related to a variety of oral and non-oral diseases (149, 150), HIV to AIDS and the associated oral pathoses (23, 149), and papillomaviruses to genital and oropharyngeal cancers (110, 135). Vaccination against smallpox virus and poliovirus has become the most successful public health measure ever in preventive medicine.

During acute viral infections, large amounts of virions are aerosolized or shed into the respiratory tract, feces, saliva or other biological fluids, and pose a risk for individuals in close contact (149, 151). Paramyxoviruses, influenza viruses, respiratory syncytial virus, niphavirus and Ebola virus are spread by aerosols (33, 71, 92, 97, 184). Relatively few viruses are transmitted from lesions of the skin, but herpes simplex virus type 1 infection is commonly acquired through labial contact (4, 18, 60). HIV, papillomaviruses and herpes simplex type 2 are examples of sexually transmitted viruses. Cytomegalovirus can be transmitted transplacentally from mother to child and give rise to preterm birth and pre-eclampsia (52, 183).

Viruses infecting oral, gastric, dermal, respiratory or genital sites encounter skin or mucosa as the first barrier for entrance (Fig. 1). The mild acidic and dry environment of the skin makes it difficult for most viruses to establish infection. The oral mucosa is thinner than the skin, and is wet but covered with mucins, immunglobulins and other protective factors in saliva. Saliva of cytomegalovirus-positive subjects possesses a neutralizing activity compared with saliva of seronegative subjects (134). Herpesviruses usually enter the host through minor breaks or abrasions of the skin or mucosa and replicate productively in epidermis or dermis, fibroblasts, macrophages and neural ending cells (16, 37, 39, 59, 68, 87, 166, 168). Papillomaviruses can replicate in skin cells and in mucosal cells. Respiratory and enteric viruses can infect and replicate in epithelial cells without requiring a break of the mucosal barrier (16, 33, 92, 132).

Herpesviruses may cause illness by mechanisms that are direct, indirect or immune-response linked, and illnesses range from subclinical or mild disease to encephalitis, pneumonia and other potentially lethal infections, and even to lymphoma, sarcoma and carcinoma (18, 40, 59, 60, 70, 104, 135, 150, 165). Several herpesvirus species are present in the saliva of most individuals, and are usually acquired through salivary contact early in life (151). Epstein–Barr virus can replicate in salivary glands and be released into saliva (5, 37, 149, 151, 166). Salivary Epstein–Barr virus and cytomegalovirus can also originate from periodontitis lesions (136, 150, 151). In the oral cavity, herpesviruses are involved in acute gingival infections, destructive periodontal disease, apical periodontitis, ulcerations of mucosa, odontogenic cyst, giant cell granuloma, autoimmune disease and various types of neoplasm (7, 41, 70, 104, 133, 135, 138, 150, 155, 165).

Periodontitis is associated with a wide range of bacteria and viruses and with complex humoral and cellular immune responses. *Porphyromonas gingivalis*, *Tannerella forsythia*, *Aggregatibacter actinomycetemcomitans*, *Treponema denticola* and some newly identified unculturable species are

CASE REPORT

Rapidly Progressive Periodontal Disease Associated with Human Immunodeficiency Virus

Khalid Al-Hezaimi[1,2], Fawad Javed[1], Tazeen Saeed Ali[3], Mansour Al-Askar[1,2] and Abdulaziz Al-Rasheed[1,2]

ABSTRACT

Severe periodontal inflammation with generalized dental plaque accumulation, spontaneous and severe gingival bleeding, fungal infection, and interdental papillae necrosis are presented in a patient infected with human immunodeficiency virus (HIV). Bite-wing radiographs revealed a generalized horizontal alveolar bone loss of 7-8 millimetres in both arches. Erythematous patches were noted on the gingival mucosa in both jaws. DNA testing was performed to indentify the periodontopathogens. The patient had no signs or symptoms of acquired immunodeficiency syndrome. This case-report presents the massive periodontal destruction that occurred in a patient infected with HIV. Therefore, it is highly recommended that patients infected with HIV should be regularly monitored to aid in early detection and to provide proper management of periodontal inflammatory conditions to minimize its destruction.

Key words: *Periodontitis. HIV-AIDS. Interdental papillae necrosis. Periodontal bone loss.*

INTRODUCTION

Periodontal inflammatory disorder may either be a slowly progressive or rapidly progressive disease. If left undiagnosed and untreated in its early stages, rapidly progressive periodontal disease may cause alveolar bone destruction and ultimately tooth loss at an alarming rate.

Rapidly progressive periodontal disease is a common manifestation in immunocompromised patients particularly those infected with Human Immuno-deficiency Virus (HIV) in comparison to periodontal disease in HIV-negative individuals.[1-3] The group of disorders affecting individuals infected with HIV is predominantly notable since oral manifestations are usually the first clinical expressions of the viral infection.[1] There are many established oral manifestations of HIV including oral candidiasis, oral leukoplakia and periodontal disease. In a recent study, Paster *et al.* reported a diverse variety of microbes associated with the development of periodontal diseases in HIV-positive patients which differ from the typical periodontal pathogens such as *Porphyromonas gingivalis (P. gingivalis)*.[4] Mechanical plaque removal and oral hygiene maintenance are important steps in healing periodontal inflammatory conditions.[5]

In the present report, we describe a case of an unusual rapidly progressive periodontal disease and necrotizing ulcerative periodontitis in a HIV-positive individual.

CASE REPORT

A 49-year-old male reported with a 10-year history of infection with the HIV. The patient also reported a three-year history of loss of vision, renal failure, and hypertension.

The patient presented with severe pain, ulcerated gingival papillae, mobile teeth and fetor oris. A comprehensive full-mouth periodontal examination revealed the presence of severe periodontal inflammatory conditions with a generalized dental plaque accumulation and spontaneous gingival bleeding on gentle probing. Necrotizing ulcerative periodontitis manifests as a rapid necrosis and destruction of the gingiva and periodontal attachment apparatus. White and erythematous patches were observed on the gingival mucosa in both jaws (Figure 1). These white patches were gently scraped off and a light microscopic investigation revealed the presence of fungal hyphae. At the first-visit full-mouth peri-apical and bite-wing radiographs were taken (Figure 2). The radiographs showed the bone level to be at the cementoenamel junction. However, at the one year follow-up, the radiographs displayed an aggressive and generalized horizontal alveolar bone loss of 7-8 millimetres in both arches (Figure 3).

Subgingival plaque was collected using absorbent paper points and a polymerase chain reaction-based test (Micro-IDent HAIN Lifescience GmbH, Nehren, Germany)

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Periodontal disease in HIV/AIDS

Mark I. Ryder, Wipawee Nittayananta, Maeve Coogan, Deborah Greenspan & John S. Greenspan

Since the early 1990's, the face of HIV infection and the AIDS global epidemic have changed significantly. Although the death rate from AIDS among 25- to 44-year-old adults has shown a marked decline in the USA and in other developed countries, largely because of newer antiretroviral therapies and improved access to these therapies, AIDS remains one of the leading causes of premature death, particularly in the developing world. The total number of new cases of HIV infection worldwide has remained relatively constant from 2006 to 2011 with approximately half of all HIV-infected individuals receiving some form of antiretroviral therapy (97). Therefore, despite the recent advances in antiretroviral therapy and prevention of HIV infection, dental and other healthcare practitioners will be required to continue to treat oral and periodontal conditions unique to HIV/AIDS as well as conventional periodontal diseases in the HIV-infected patient.

In order to present the full scope of the epidemiological and clinical issues involved in HIV-associated oral and periodontal diseases and conditions of infection in the developing world, we discuss the current clinical and epidemiological trends of HIV infection in general, and the oral and periodontal manifestations of HIV infection in both the developing and developed worlds, in both adults and children. This is followed by a brief update on recent insights into the microbiology and pathogenesis of periodontal diseases in HIV-infected patients, and their implications for diagnosis and treatment in the antiretroviral therapy era in developing and developed countries. The current standard accepted therapies for the treatment of both the uncommon periodontal lesions seen with greater frequency in HIV infection, and the more common periodontal diseases in both developing and developed countries are then discussed. The concluding section of this paper will discuss the broad implications of the current state of knowledge of HIV infection and oral/periodontal diseases in the developing world, and provide recommendations for future epidemiological, basic science and clinical investigations.

Trends of HIV infection and AIDS in the developing and the developed worlds

HIV infection and AIDS continue to have catastrophic global medical and social effects, especially in regions where the prevalence is relatively high, such as in sub-Saharan Africa, Central and South-East Asia, eastern Europe and South America. More than 60 million people have been infected with HIV worldwide. More than 30 million have died, and 34 million are currently living with HIV infection (168).

However, the growth rate of the pandemic appears to have plateaued since the first case of AIDS was reported by the US Centers for Disease Control and Prevention in year 1981 (20, 97). In 2009, an estimated 2.6 million people became newly infected with HIV, which is nearly one-fifth (19%) fewer than the 3.1 million new cases in 1999. In sub-Saharan Africa, the estimated 1.8 million people who became infected in 2009 is lower than the estimated 2.2 million new cases in 2001 (168).

However, some other parts of the world do not fit this overall declining trend. For example, Central Asia, defined by the World Health Organization as the Republics of Kazakhstan, Kyrgyzstan, Uzbekistan, Tajikistan and Turkmenistan, is experiencing one of the fastest growing HIV epidemics in the world (177). Following the collapse of the Soviet Union, there has been a rise in sex work and injection drug use, both risk factors associated with the HIV infection. High rates of HIV transmission in this region continue to occur among injecting drug users and their sexual partners (160).

A combination of factors, including the impact of HIV-prevention efforts and the scientific progress in HIV/AIDS research, especially in the development of

Original Article

Periodontal pocket as a potential reservoir of high risk human papilloma virus: A pilot study

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Abstract:

Aim: Human papilloma viruses (HPVs) are small DNA viruses that have been identified in periodontal pocket as well as gingival sulcus. High risk HPVs are also associated with a subset of head and neck carcinomas. HPV detection in periodontium has previously involved DNA detection. This study attempts to: (a) Detect the presence or absence of high risk HPV in marginal periodontiun by identifying E6/E7 messenger RNA (mRNA) in cells from samples obtained by periodontal pocket scraping. (b) Detect the percentage of HPV E6/E7 mRNA in cells of pocket scrapings, which is responsible for producing oncoproteins E6 and E7. **Materials and Methods:** Pocket scrapings from the periodontal pockets of eight subjects with generalized chronic periodontitis were taken the detection of presence or absence of E6, E7 mRNA was performed using *in situ* hybridization and flow cytometry. **Results:** HPV E6/E7 mRNA was detected in four of the eight samples. **Conclusion:** Presence of high risk human papillomaviruses in periodontal pockets patients of diagnosed with chronic periodontitis, not suffering from head and neck squamous cell carcinoma in the present day could link periodontitis to HPV related squamous cell carcinoma. Prevalence studies are needed detecting the presence of HPV in marginal periodontium as well as prospective studies of HPV positive periodontitis patients are required to explore this possible link.

Key words:

E6/E7 messenger RNA, head and neck carcinoma, human papilloma virus, periodontal pocket

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INTRODUCTION

Papilloma viruses are epitheliotropic DNA viruses[1] associated with several benign conditions including condylomata acuminatum, focal epithelial dysplasia, respiratory papillomatosis,[2] and gingival warts.[3,4] It has been known since the 1990s that papillomaviruses cause cervical cancer.[5]

Of late, these viruses have also been implicated in the etiology of a growing subset head and neck cancers, specifically the oropharynx and the base of tongue, numerous cases of which have been reported all over the world[6-8] despite increasing awareness about the hazards of tobacco use. High-risk human papilloma virus (HPV) genotypes such as HPV-16, HPV-18, HPV-31, and HPV-33 have been found to be associated with these cancers.[9] The significance of the increased incidence of head and neck carcinomas caused by human papillomaviruses is reflected by the fact that human squamous cell carcinomas have now been divided into two subsets: Tobacco related squamous cell carcinomas and HPV related squamous cell carcinomas.[10-12]

Of rising concern, importance is the fact that high risk human papillomaviruses have been detected in the periodontium of patients diagnosed with chronic periodontitis as well as those with healthy gingiva.[13] It has even been thought that sites in close proximity to tongue and oropharynx may serve as reservoirs for high risk human papillomaviruses[14] which may include periodontal pockets or gingival sulci of mandibular posterior teeth.

HPV E6, E7 oncoproteins mediate the development of cancer. Their overexpression can be measured as E6, E7 messenger RNA (mRNA) transcripts.[15]

Previous studies have used HPV DNA testing methods to identify HPV in the periodontium which provide adequate sensitivity but lack specificity. This pilot study attempts to detect high risk HPVs in marginal periodontium by

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Periodontitis and oral human papillomavirus infection among Hispanic adults

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ABSTRACT

Introduction: Research on the association between periodontitis and oral human papilloma virus (HPV) infection is inconsistent. The cross-sectional association of severe periodontitis with oral HPV infection was investigated in a sample of Hispanic adults.

Methods: Data from the 2014–2016 San Juan Overweight Adults Longitudinal Study (n = 740) was analyzed. Periodontitis assessment and self-collection of oral HPV samples followed the National Health and Nutrition Examination Survey methodology. Periodontitis was defined using the Centers of Disease Control and Prevention/American Academy of Periodontology definition. HPV typing was performed using polymerase chain reaction. Multivariate logistic regression models were used to calculate odds ratios (ORs) and 95% confidence intervals (CIs).

Results: 5.7% of participants had oral HPV infection and 20.3% had severe periodontitis. Adults with severe periodontitis had higher odds of oral HPV infection than those with none/mild disease (OR = 2.9, 95% CI: 1.0–8.4, $p < 0.05$) in multivariable analysis. Adults with clinical attachment loss ≥ 7 mm and pocket depth PD ≥ 6 mm had 2- to 3-fold higher odds of HPV infection.

Conclusions: Severe periodontitis was positively associated to oral HPV infection. Longitudinal evaluation of periodontal inflammation's role in acquisition and persistence of oral HPV infection is needed, as periodontitis screening could identify individuals at increased risk of HPV-related oral malignancies.

1. Introduction

Head and neck squamous cell carcinoma (HNSCC) includes squamous cell cancers of the nasal cavity, the paranasal sinuses, the oral cavity, the pharynx (includes the nasopharynx, oropharynx and hypopharynx) and the larynx [1]. Although high-risk (oncogenic) human papilloma virus (HPV) sub-types have been detected in HNSCC, viral infection appears to be more strongly associated to oropharyngeal cancers, particularly those in the palatine and lingual tonsils and the base of the tongue [1–3]. HPV-positive oropharyngeal cancers are increasing [2] and molecular studies have linked this increase to HPV [2]. Nonetheless, the epidemiology and natural history of oral HPV infection is still not well understood [1]. While the prevalence of HPV in oropharyngeal cancers has increased, with estimates of 72% in North America, Europe and other populations [4], prevalence of oral HPV infection in cancer-free individuals, risk factors, natural history, and transmission mechanisms remain largely unexplored. In the US, prevalence estimates of oral HPV infection were 6.9% in 2009–2010 [5] and 8.1% during 2009–2012 [6]. Oral sex, male gender, older age, open-mouthed kissing, increasing number of sexual partners, HIV infection, tobacco, and marijuana and heavy alcohol use have been associated with oral HPV infection [5,7,8].

Although research suggests an association between chronic oral inflammation, including periodontitis, oral HPV infection, and various HNSCC [9–11], particularly oropharyngeal cancers, studies on the relationship of oral HPV infection with these chronic conditions are

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Review

How Does Epstein–Barr Virus Contribute to Chronic Periodontitis?

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Abstract: Chronic periodontitis is spreading worldwide and mutually interacts with systemic diseases like diabetes mellitus. Although periodontopathic bacteria are inevitable pathogens in their onset and progression, many cases are not ascribable to the virulence of these bacteria because the effect of plaque control is limited. In contrast, Epstein–Barr virus (EBV) in the periodontium has been correlated with chronic periodontitis and has recently been considered as a promising pathogenic candidate for this disease. However, several important questions have yet to be addressed. For instance, although EBV latently infects more than 90% of individuals over the world, why do patients with chronic periodontitis exclusively harbor progeny EBV in the oral cavity? In addition, how does latently infected or reactivated EBV in the periodontium relate to the onset or progression of chronic periodontitis? Finally, is periodontitis incurable because EBV is the pathogen for chronic periodontitis? In this review, we attempt to answer these questions by reporting the current understanding of molecular relations and mechanisms between periodontopathic bacteria and EBV reactivation in the context of how this relationship may pertain to the etiology of chronic periodontitis.

Keywords: Epstein–Barr virus; chronic periodontitis; periodontopathic bacteria; microbial interaction; periodontopathic virus

1. Introduction

Epstein–Barr virus (EBV), a gamma-herpesvirus, latently infects more than 90% of adult humans worldwide [1]. However, some cases of EBV infection cause clinical manifestations including infectious mononucleosis, autoimmune disorders, and a number of malignancies including Burkitt's lymphoma, Hodgkin's disease, nasopharyngeal carcinoma, and gastric adenocarcinoma [1]. Like other herpesviruses, EBV establishes a persistent infection in the host during which it has latent and lytic phases [1,2]. EBV is transmitted from person to person via saliva and passes through the oropharyngeal epithelium to B lymphocytes, where it establishes a lifelong latent infection but is sometimes reactivated unpredictably to cause life-threatening diseases [1,2]. Elucidation of the molecular mechanisms involved in maintaining and disrupting EBV latency (EBV reactivation) has therefore been a central topic of EBV research.

Chronic periodontitis, a complex, chronic inflammatory disorder that involves interactions of specific bacterial pathogens and host cellular responses, is among the most prevalent microbial diseases in humans [3,4]. Severe chronic periodontitis results in the loosening of teeth, occasional pain and discomfort, impaired mastication, and eventual tooth loss. Specific bacterial species, mostly Gram-negative bacteria such as *Porphyromonas gingivalis*, *Fusobacterium nucleatum*, *Tannerella forsythia*, and *Treponema denticola* show a close association with periodontitis (Figure 1) [3,4].

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Short review

Herpesviruses in human periodontal disease

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Recent studies have identified various herpesviruses in human periodontal disease. Epstein–Barr virus type 1 (EBV-1) infects periodontal B-lymphocytes and human cytomegalovirus (HCMV) infects periodontal monocytes/macrophages and T-lymphocytes. EBV-1, HCMV and other herpesviruses are present more frequently in periodontitis lesions and acute necrotizing ulcerative gingivitis-lesions than in gingivitis or periodontally healthy sites. Reactivation of HCMV in periodontitis lesions tends to be associated with progressing periodontal disease. Herpesvirus-associated periodontitis lesions harbor elevated levels of periodontopathic bacteria, including *Actinobacillus actinomycetemcomitans*, *Porphyromonas gingivalis*, *Bacteriodes forsythus*, *Prevotella intermedia*, *Prevotella nigrescens* and *Treponema denticola*. It may be that active periodontal herpesvirus infection impairs periodontal defenses, thereby permitting subgingival overgrowth of periodontopathic bacteria. Alteration between latent and active herpesvirus infection in the periodontium might lead to transient local immunosuppression and explain in part the episodic progressive nature of human periodontitis. Tissue tropism of herpesvirus infections might help explain the localized pattern of tissue destruction in periodontitis. Absence of herpesvirus infection or viral reactivation might explain why some individuals carry periodontopathic bacteria while still maintaining periodontal health. Further studies are warranted to delineate whether the proposed herpesvirus-periodontopathic bacteria model might account for some of the pathogenic features of human periodontal disease.

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Key words: herpesvirus; human cytomegalovirus; Epstein–Barr virus; herpes simplex virus; polymerase chain reaction; periodontal disease

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Most human viruses known to cause oral diseases are DNA viruses that are contracted in childhood or early adulthood through contact with blood, saliva or genital secretions (1). Herpesviruses seem to be the most important DNA viruses in oral pathology. The hallmark of herpesvirus infections is immune impairment. Active herpesvirus infections may have particularly severe consequences in HIV-infected and other immunocompromised individuals.

Eight herpesvirus species have been identified (Table 1). Oral disease has been attributed to herpes simplex virus (HSV) type 1 (2, 3), HSV type 2 (3, 4), varicella-zoster virus (VZV) (5, 6), Epstein–Barr virus (EBV) (3, 7), human cytomegalovirus (HCMV) (2, 8, 9) and human herpes virus 8 (HHV-8) (10). Active herpesvirus infection in the oral cavity often involves ulceration of gingiva (3, 7, 11). Recent studies have implicated EBV-1 and HCMV in the pathogenesis of human periodontal disease (12, 13). The present review describes the association between herpesviruses and periodontal disease and discusses possible mechanisms by which herpesviruses might contribute to periodontal disease.

General description of herpesviruses

Herpetoviridae

The Herpetoviridae family contains only the genus Herpesvirus. Herpesviruses share at least four characteristics: 1) the typical particle morphology consists of an icosahedral capsid assembly of 162 capsomers enclosed in a viral envelope; 2) the genome comprises a single double-stranded DNA molecule ranging in size from 120 to 250 kbp; 3)

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Detection of Virus Herpes Simplex Type 1 in Patients with Chronic Periodontal Disease

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Keywords: Periodontal disease; HSV-1; Multiplex PCR

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Abstract

BACKGROUND: Periodontal disease is an inflammatory-destructive condition of the supporting tissues of the teeth. Microorganisms found in the dental plaque were considered to be the primary local etiologic factor responsible for the periodontal destruction. It is also evident that herpes simplex viruses may have an impact in the etiopathogenesis of periodontal disease.

AIM: This study has been made with the aim to analyse the prevalence of herpes simplex virus type 1 (HSV-1) in the dental plaque (supra- and subgingival) of patients with the chronic periodontal disease.

MATERIAL AND METHODS: The study comprised a total of 89 patients with chronic periodontal disease divided into two groups (patients with moderate and severe periodontitis). Supragingival dental plaque samples were taken with sterile cotton (supragingival), and subgingival dental plaque samples were taken with paper absorbents. Samples were subjected to extraction of DNA and further analysis with multiplex PCR for the presence of herpes viral DNA.

RESULTS: HSV-1 virus was detected In 24.7% of all patients included in the study. HSV-1 was detected in 22.2% of patients with the moderate stage of the disease, of which in all (100%) in the supragingival plaque samples and only 16.7% in subgingival plaque samples. In two patients HSV-1 was concomitantly detected in supra and subgingival plaque samples. In patients with advanced stage of the disease, the HSV-1 virus was detected in 28.6% patients. In two of the patients, HSV-1 was concomitantly detected in supra and subgingival plaque samples. Statistically, a significant difference was found in HSV-1 positive patients with a moderate stage of disease, between the presence of the virus in subgingival (100%) and subgingival (16.7%) dental plaque samples, $p < 0.05$.

CONCLUSION: Herpes simplex viruses type 1 are present in supragingival and subgingival dental plaque.

Introduction

Periodontitis is the most common form of the oral disease in adults; this disease is an inflammatory-destructive condition of the supporting tissues of the teeth, it is considered to be a result of many factors.

For many years microorganisms found in the dental plaque were considered to be the primary local etiologic factor responsible for the periodontal destruction, so a number of putative bacteria as *Porphyromonas gingivalis, Tannerella forsythia* and *Aggregatibacter actinomycetemcomitans* is considered to be associated with the periodontal disease and are used as diagnostic markers [1] [2]. Clinical features of this commonly encountered disease are a result of interaction between microorganisms and the host immune response. It is evident that host immune responses against infection with bacteria and the subsequent production of proinflammatory cytokines are of particular importance in periodontium destruction [3] [4]. Microorganisms initiate inflammatory reactions in the periodontium, which causes in long run loose teeth, destruction of

REVIEW ARTICLE

Are herpes virus associated to aggressive periodontitis? A review of literature

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ABSTRACT

Periodontal Disease includes a wide variety of infectious entities with various clinical manifestations in the oral cavity and responses to treatment. The determinants of clinical manifestations of periodontal disease include the type of infectious agent, the host immune response and environmental factors. Aggressive periodontitis (AP) is defined as a type of inflammation with specific clinical and laboratory features, which distinguish it from other types of periodontitis, with high incidence rates in a sub-group of individuals. Bacteria have been frequently mentioned as the agent inciting gingival inflammation and tissue destruction that underlies the pathogenesis of periodontitis. However, recent studies, with some controversial results, have suggested that the herpes family of viruses, including CMV and EBV-1 as well as papillomaviruses, HIV, Human T-lymphotropic virus type 1, Torquetenovirus and hepatitis B and C occur with high frequency in active periodontal lesions. There is a lack of information about this disease and the role of herpesviruses in its pathophysiology. This review provides a critical analysis of the scientific evidence linking bacteria and viruses with AP and their potential impact on clinical characteristics, prognosis and therapy.

Key words: Aggressive periodontitis, herpes viruses, periodontal microorganisms

INTRODUCTION

Aggressive periodontitis (AP) with a prevalence between 0.1% and 1.0% in European Caucasians, affects a minority of patients but is consider as a severe disease regardless the serious damage that can lead to early tooth loss.[1,2] The AP is characterized by the quick loss of insertion and the bone destruction. It usually affects young people who do not have a significant medical history and can show a familial aggregation of cases.[1-3]

Clinical characteristics of aggressive periodontitis

The AP is less frequent than chronic periodontitis and mainly affects young patients, however, it can occur at any age.[3] This implies that the etiologic agents have been able to cause clinically detectable disease levels in a relatively short period of time. This is important for the current understanding of these diseases since it involves an infection with a highly virulent microflora and/or a high level of the individual susceptibility to the AP disease.[3-5]

The environmental factors play a key role in the expression of this type of periodontitis. These factors involve tobacco smoke (disturbs the relationship between host and parasite leading to the worst levels of clinical parameters and limits the success of treatment resulting in negative prognosis), oral hygiene (although in many cases, the quantity of microbiological

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Human Cytomegalovirus and Epstein–Barr Virus in Apical and Marginal Periodontitis: A Role in Pathology?

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Periodontitis is presumably caused by bacterial infection, but it has been shown recently that affected tissue often contains human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV). The present study was initiated to evaluate the role of these viruses in the pathogenesis of periodontitis. HCMV and EBV were quantified in 40 apical and 25 marginal periodontitis samples using real time PCR. In situ hybridization or immunohistochemistry was carried out on apical samples to detect viral presence within cells. A possible association with relevant bacteria was examined. Of the apical periodontitis samples, 50% contained EBV, while none contained HCMV. Of the marginal periodontitis samples, 40% were positive for EBV and 12% for HCMV. With one exception, however, the amount of virus was close to the detection limits. EBV was only detected in 1 out of 15 healthy periodontium samples. Immunohistochemistry and in situ hybridization were all negative. Significant associations were found between periodontal EBV and the presence of *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis*. Although there was an obvious association of the virus with clinical samples, it seems unlikely that these viruses play a major role in the pathogenesis of periodontitis of the average patient. Their presence may reflect that the clinical samples contain more blood or saliva compared to controls, or an accumulation of lymphoid cells harboring virus in the inflamed tissue. ***J. Med. Virol. 80:1007–1011, 2008.***

KEY WORDS: Epstein–Barr virus; cytomegalovirus; apical periodontitis; marginal periodontitis; quantitative PCR; in situ hybridization

INTRODUCTION

It is well documented that apical and marginal periodontitis are associated with bacteria colonizing the root/tooth surfaces [Kakehaski et al., 1965; Socransky and Haffajee, 2002]. Recently, however, it has been shown that these lesions often contain viruses of the herpes family, particularly human cytomegalovirus (HCMV) and Epstein–Barr virus (EBV) [for reviews see Slots, 2004; Cappuyns et al., 2005; Slots et al., 2006]. Virus and bacteria may act in synergy to produce pathology. Slots et al. [2006] suggested that herpesviruses can influence the development and course of periodontitis, while Cappuyns et al. [2005] are skeptical.

Both EBV and HCMV are present latently in the vast majority of the adult population. EBV is primarily harbored in B cells and in epithelial cells of the oropharynx, while HCMV is present in a greater variety of cells including various epithelial cells, endothelical cells, and leukocytes. Both viruses are active periodically and shed viral particles to the saliva.

Active replication in periodontal tissues can be envisaged easily to impact the immune response in a way that benefits both opportunistic bacteria and the virus, and thus lead to aggravated symptoms. For example, the viruses produce cytokine mimics designed to modulate immune defense. On the other hand, the presence of virus in affected tissues does not prove an active role, it may just reflect normal viral replication. It should also be noted that microbial activity can induce

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Epstein–Barr virus is associated with periodontal diseases

A meta-analysis based on 21 case–control studies

Zilong Gao, MD[a], Juan Lv, MD[c,d,*], Min Wang, PhD[b]

Abstract

Some controversies still exist between the detection of Epstein–Barr virus (EBV)'s DNA and risks of periodontal diseases. Hence, a comprehensive meta-analysis on all available literatures was performed to clarify the relationship between EBV and preidontitis.

A comprehensive search was conducted within the PUBMED, EMBASE, and WANFANG databases up to October 10th, 2016 according to inclusion and exclusion criteria and finally 21 case–control literatures were obtained. The outcomes including odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of associations. Publication bias was determined by Begg or Egger test. Sensitivity analysis was used to investigate reliability and stability of the results.

According to the data from included trials, the association between overall increased risks of periodontitis and the detection of EBV was significant (OR=6.199, 95% CI=3.119–12.319, $P<0.001$). In the disease-type analysis, the pooled ORs for chronic periodontitis and aggressive periodontitis were 6.586 (95% CI=3.042–14.262, $P<0.001$) and 8.361 (95% CI=2.109–33.143, $P=$ 0.003), respectively. In the subgroup analysis of ethnicity, our results suggested that high EBV-detecting frequencies were correlated with increased risks of periodontitis in Asians, Europeans, and Americans ($P<0.001$). Subgroup analysis by the sample type showed that subgingival plaque (SgP) samples and tissue samples were available for EBV detecting ($P<0.001$). Detecting EBV of samples in ≥5 (6) mm sites of periodontal pockets were easier than in ≤3-mm sites ($P=0.023$).

This meta-analysis indicates that high frequent detection of EBV correlates with increased risk of periodontal diseases. SgP and tissue are available for detecting EBV in patients of periodontitis. At last, our results suggest that detecting EBV of samples in =5 (6) mm sites of periodontal pockets are more sensitive than in ≤3-mm sites.

Abbreviations: AgP = aggressive periodontitis, CI = confidence interval, CP = chronic periodontitis, EBV = Epstein-Barr virus, GCF = crevicular fluid, HHV-4 = human herpesviruses 4, OR = odds ratio, pECs = epithelial cells of periodontium, SgP = subgingival plaque.

Keywords: EBV, Meta-analysis, periodontal diseases

1. Introduction

Periodontitis is a chronic inflammatory disease that is characterized by periodontal damage, alveolar bone resorption, pain, and eventual tooth loss.[1] The pathogenesis of periodontitis is considered to involve complex interactions between microbial factors, host factors, and a variety of environmental factors.[1] The subgingival plaque is required for the initiation of the disease.[2] Interestingly, several studies suggested that the current theory of bacterial plaque cannot explain that patients who are absent of these specific bacterial species still got periodontal diseases.[3,4] And no significant difference in the prevalence of bacteria between healthy and diseased periodontal tissues has been found.[5] Therefore, human herpesviruses have been found to be involved in the etiology of periodontitis because bacterial activity alone is not able to explain all the clinical characteristics of periodontal diseases.[6]

EBV, also called human herpesviruses 4 (HHV-4), belongs to γ-herpes virus subfamilies. EBV has widely infected >90% adults in the world and is associated with many human diseases, such as post-transplate lymphoproliferative diseases, nasopharyngeal carcinoma, and oral hairy leukoplakia.[7] The first report about the relationship between EBV and chronic periodontitis (CP) came into our sight in 1996.[8] Afterwards, a number of articles[9–29] have investigated the associations between EBV and periodontal diseases including CP and aggressive periodontitis (AgP). However, these findings were full of controversy among detecting EBV existence in the periodontal environment. Some studies[10–12,14,15,17–23,26–29] have reported that with high prevalence of EBV DNA detecting, the risks of periodontal diseases are significantly increased; whereas others[9,13,16,24,25] suggested a weak or even no relationship between them. Hence, we performed the current comprehensive meta-analysis, which combines results from literatures to confirm whether the EBV is associated with periodontal diseases.

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The authors report no conflicts of interest.

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Epstein–Barr virus reactivation by persistent apical periodontal pathogens

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Abstract

Himi K, Takeichi O, Imai K, Hatori K, Tamura T, Ogiso B. Epstein–Barr virus reactivation by persistent apical periodontal pathogens. *International Endodontic Journal*, **53**, 492–505, 2020.

Aim To assess whether Epstein–Barr virus (EBV) reactivation is triggered by persistent apical periodontitis-related microbes using *in vitro* and *ex vivo* methodologies.

Methodology Surgically removed human periapical granulomas ($n = 50$) and healthy gingival tissues ($n = 10$) were analysed to determine the presence of EBV and seven persistent apical periodontitis-related microbes. In addition, real-time polymerase chain reaction was used to detect the mRNA expression of BZLF-1, an immediate–early gene of EBV. Expression of latent membrane protein (LMP)-1 and ZEBRA, an early lytic protein of EBV encoded by BZLF-1, was also examined using triple-colour immunofluorescence staining. *n*-Butyric acid produced by the microbes was quantified, and luciferase assays were performed in association with bacterial lysates. In addition, Daudi cells were cultured with bacterial lysates, and the expression levels of BZLF-1 mRNA and ZEBRA protein were determined.

Results EBV DNA and BZLF-1 mRNA were detected in 47 out of 50 periapical granulomas, but not in healthy gingival tissues. The EBV DNA copy number and the number of *Fusobacterium nucleatum* were significantly positively correlated with BZLF-1 expression in periapical granulomas. The number of *Prevotella intermedia* was slightly correlated with BZLF-1 expression; however, the other microbes were not. CD79a-positive B cells in periapical granulomas, but not those in healthy gingival tissues, expressed both LMP-1 and ZEBRA. *n*-Butyric acid production was the highest in *F. nucleatum* and the lowest in *P. intermedia*. *Enterococcus faecalis*, *Candida albicans* and the other tested microbes did not produce *n*-butyric acid. An *F. nucleatum* lysate exhibited significantly increased BZLF-1-luciferase activity in the same manner of commercial butyric acid, whereas *P. intermedia* did not. *F. nucleatum* also induced the expression of BZLF-1 mRNA and ZEBRA protein by Daudi cells, indicating that EBV reactivation was induced.

Conclusion Among the persistent apical periodontitis-related bacteria that were tested, *F. nucleatum* most strongly reactivated latent EBV, whereas *E. faecalis* and *C. albicans* as well as the other microbes did not.

Keywords: butyric acid, histone deacetylase inhibitor, human herpesvirus 4, periapical granuloma, persistent periapical periodontitis.

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Introduction

Epstein–Barr virus (EBV) is a human herpesvirus first discovered in lymphoblasts from patients with Burkitt lymphoma (Epstein *et al.* 1964). It was then found in other malignancies, including nasopharyngeal carcinoma (Henle & Henle 1970), and in nonmalignant diseases such as infectious mononucleosis (Diehl *et al.*

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Gingival and periodontal alterations associated with infection with human immunodeficiency virus*

Angelika Langford**

Various changes may occur in the gingiva and/or the periodontium as an expression of existing infection with human immunodeficiency virus. Thus, periodontal disease, characterized by unusual course, progress, and resistance to treatment, may occur with increased frequency. Clinically, pseudomembranous or erythematous (atrophic) forms of candidiasis or so-called papillary hyperplasia may be caused by ubiquitous fungi. Although Candida albicans *infections arise frequently on the cheek, the palate, the dorsum of the tongue, and the corner of the mouth (angular cheilitis), gingivo-periodontal manifestation is more unusual. Because of the existing immune defect, infection with or reactivation of various viruses may occur. Recurrent, progressive destructive ulcerations may be caused by herpes simplex virus 1 or 2, but apparently limited ulcerations may be an expression of a disseminated cytomegalovirus infection. Oral Kaposi's sarcoma appears initially as bluish or reddish spots; these may transform during the course of the disease into blue, occassionally lymphoma-like or lymphangioma-like, exophytic tumors.* (Quintessence Int *1994;25:375–387.*)

Introduction

Occurrence of unusual disease of the lungs from *Pneumocystis carinii* together with Kaposi's sarcoma in young homosexual men led, in 1981, to definition of the acquired immunodeficiency syndrome (AIDS). Homosexual and bisexual men, intravenous-drug abusers, and hemophiliacs requiring substitution therapy appeared to be affected most often. The obvious association of the disease with specific population groups made a viral cause probable early on. A previously unknown retrovirus was grown at the Institut Pasteur in Paris from the lymph nodes of a diseased patient. In quick succession, numerous similar isolates were described, particularly in the United States. In 1986, these viruses were given the name *human immunodeficiency virus type 1 (HIV 1)* for the sake of standardization of the nomenclature. In the same year, HIV 2, a virus with little similarity to HIV 1, was isolated for the first time from West African patients. Today HIV 1 and HIV 2 are recognized as the cause of AIDS.

The manifold clinical symptoms of this disease are explained by the special affinity of HIV to a certain surface structure of the cell membrane (CD4 receptor). Such surface structures have been demonstrated on cell types as diverse as cells of the immune system (T-helper lymphocytes, monocytes, macrophages, Langerhans cells, and β-lymphocytes), endothelial cells, and nerve cells during the past several years. This specialized surface facilitates adhesion and penetration of the HIV into the body cells. There, it can lead to viral integration into the host-cell genome, viral replication, and release (Fig 1). The lifelong persistence of HIV in an infected cell complicates all therapeutic efforts.

Clinically, the disease manifests as the collapse of cell-transmitted immunity and thus the ability of the

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Original Article

High risk human papillomavirus in the periodontium : A case control study

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Abstract:

Background: Human papilloma viruses (HPVs) are small DNA viruses that have been identified in periodontal pocket as well as gingival sulcus. High risk HPVs are also associated with a subset of head and neck carcinomas. It is thought that the periodontium could be a reservoir for HPV.Aims:1.Detection of Human Papilloma virus (HPV) in periodontal pocket as well as gingival of patients having localized chronic periodontitis and gingival sulcus of periodontally healthy subjects.2.Quantitative estimation of E6 and E7 mRNA in subjects showing presence of HPV3.To assess whether periodontal pocket is a reservoir for HPV.Settings and Design: This case-control study included 30 subjects with localized chronic Periodontitis (cases) and 30 periodontally healthy subjects (controls). Two samples were taken from cases, one from periodontal pocket and one from gingival sulcus and one sample was taken from controls. **Methods and Materials:** Samples were collected in the form of pocket scrapings and gingival sulcus scrapings from cases and controls respectively.These samples were sent in storage media for identification and estimation of E6/E7 mRNA of HPV using in situ hybridization and flow cytometry.Statistical analysis: Statistical analysis was done by using, mean, percentage and Chi Square test. A statistical package SPSS version 13.0 was used to analyze the data.P value <0.05 was considered as statistically significant. **Results:** pocket samples as well as sulcus samples for both cases and controls were found to contain HPV E6/E7 mRNAInterpretation and **Conclusion:** Presence of HPV E6/E7 mRNA in periodontium supports the hypothesis that periodontal tissues serve as a reservoir for latent HPV and there may be a synergy between oral cancer, periodontitis and HPV. However prospective studies are required to further explore this link.

Key words:

E6/E7 mRNA, humanpapillomavirus, periodontitis

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INTRODUCTION

Periodontal disease is characterized by the presence of gingival inflammation, loss of tissue attachment, periodontal pocket formation, and alveolar bone loss around the affected tooth.

It is widely accepted that the initiation and progression of periodontitis are dependent on the presence of Gram-negative and Gram-positive microorganisms capable of causing diseases.[1]

However, the traditional theories that explain the pathophysiology of periodontitis are not able to explain various aspects of the disease including the failure of progression of all cases of gingivitis to periodontitis, site specificity, its episodic nature, etc.[2] Hence, research has branched out in different directions, one of which includes viruses.

At least, three characteristics of periodontal microorganisms have been identified that can contribute to their ability to act as pathogens: the capacity to colonize, i.e., invade and reproduce in host cells, ability to evade antimicrobial host defenses mechanisms and the ability to produce substances that can directly initiate tissue destruction.[3]

Some of these properties have been found in viruses, and of late the role of viruses in the pathogenesis of periodontal disease is being investigated. This includes herpesviruses and human papillomavirus (HPV).[4-6]

Of these viruses, the HPV is of particular interest as it has been found in the oral cavity and in particular in the marginal periodontium,[7-9] and is also known to be associated with malignancies of the head and neck.[10] HPV associated head and neck carcinomas are of increasing importance and constitute a unique entity among head and neck carcinomas.[11]

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PLOS PATHOGENS

PEARLS

Virus interactions with bacteria: Partners in the infectious dance

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The outcome of viral infection depends on the interplay between host factors and the environment. Host factors, like the expression of viral receptors, convey permissiveness to infection, define tropism, regulate antiviral immune responses, determine viral clearance, and spread. The host microbiota, the constellation of microbes inhabiting an organism, also plays a key role in the outcome of infection. Microbes and microbial products can directly interact with viral particles. Our understanding of how the microbiota impacts virus infection is largely limited to the bacterial component of the microbiota. Although bacteria do not support eukaryotic virus infection, they can promote viral fitness by enhancing virion stability, promoting infection of eukaryotic cells, and increasing coinfection rates. Virus binding of bacteria can also impact bacterial biology, including bacterial adherence to eukaryotic cells. These interactions can also indirectly affect the host response to viral infection. In this Pearl, we focus on how direct and indirect interactions between viruses and bacteria impact viral biology and touch on recent findings that illustrate how bacterial biology can also be impacted by interactions with eukaryotic viruses (Fig 1).

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Direct interactions between mammalian viruses and the microbiota

The bacterial component of the microbiota can directly or indirectly impact the outcome of infection by a range of different viruses. Direct interactions have been observed between bacteria and influenza A virus (IAV) [1, 2] as well as several enteric viruses: picornaviruses (including poliovirus [3, 4]); coxsackieviruses A21, B2, B3, Echovirus 30, Mengo, and Aichi viruses [5, 6]; human noroviruses (HNoV) [7, 8]; and mammalian orthoreovirus (reovirus) [9]. Although bacteria can directly impact the outcome of infection by several viruses, the viral factors involved in the interaction between bacteria and viruses are largely undefined.

In many cases, binding of viruses to bacteria is mediated through bacterial envelope components lipopolysaccharide (LPS), the main component of the gram-negative bacterial envelope, and peptidoglycan (PG), the main component of the gram-positive bacterial envelope. Poliovirus binds to LPS and PG from several bacterial species [3–5, 10]. Although the bacterial binding epitopes for poliovirus are unknown, the virus may bind LPS, PG, and chitin through the monosaccharide N-acetyl-glucosamine (GlcNAc) [4]. HNoVs use histo-blood group antigens (HBGAs) to attach to eukaryotic cells [11] and can bind bacterial HBGAs [12]. Reovirus thermostability is enhanced by LPS and PG independent of serotype, but lipoteichoic acid, a major component of the gram-positive bacterial envelope, elevates the thermostability of only one reovirus serotype [9]. As different viral strains and serotypes differ in their interactions with bacterial envelope components, specific genetic determinants of norovirus, poliovirus, and reovirus, likely determine the use of specific bacterial components.

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Mini-review

Herpesviruses: a unifying causative factor in periodontitis?

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Slots J, Contreras A. Herpesviruses: a unifying causative factor in periodontitis? Oral Microbiol Immunol 2000: 15: 277–280. © Munksgaard, 2000.

Human cytomegalovirus and Epstein-Barr virus type 1 are discussed in this review as they relate to destructive periodontal disease in humans. Genomes of the two herpesviruses occur frequently in severe adult periodontitis, localized and generalized juvenile periodontitis, Papillon-Lefèvre syndrome periodontitis, Down's syndrome periodontitis, HIV-associated periodontitis and acute necrotizing ulcerative gingivitis. Herpesvirus infections generally involve a mild or asymptomatic primary phase followed by an asymptomatic latent phase interrupted sporadically by periods of activation, where viral replication and possibly clinical disease become manifest. Herpesvirus reactivation is triggered by a number of immunosuppressing factors, some of which have also been shown to be risk indicators of periodontal disease. Available evidence argues for the involvement of active cytomegalovirus infection in the initiation and progression of localized juvenile periodontitis and possibly other types of periodontal disease. In periodontal disease, herpesviruses may cause release of tissue-destructive cytokines, overgrowth of pathogenic periodontal bacteria, and initiation of cytotoxic or immunopathogenic events. Understanding the significance of herpesviruses in the causation and pathogenesis of destructive periodontal diseases may have important implications in future prevention and treatment of the diseases.

Key words: herpesviruses; cytomegalovirus; Epstein-Barr virus; periodontal disease; pathogenesis

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Periodontitis exhibits a waxing and waning course of progression and a variety of clinical manifestations. The disease has arbitrarily been divided into subgroups based on patient's systemic health, time of disease onset, degree of periodontal tissue destruction, rate of disease progression, percentage of affected teeth, vertical or horizontal pattern of alveolar bone destruction, response to treatment, type of associated gingivitis, type of infecting microorganisms, type of host response, etc. (14). However, it is not known whether various clinical types of periodontitis have distinct types of causation, or if a limited number of etiologic agents together with various disease-modifying factors determine the clinical appearance of the disease. Establishing the basic etiology of periodontitis is of utmost importance because the more limited the cause of the disease, the more restricted the prophylactic and therapeutic approach can be.

Recent studies have revealed an association between some of the eight known members of the herpesvirus family and destructive human periodontal disease (11). Genomes of human cytomegalovirus (HCMV) and Epstein-Barr virus type 1 (EBV-1) are frequently detected in severe adult periodontitis (9, 32), localized juvenile periodontitis (28, 46), generalized juvenile periodontitis (41), Papillon-Lefèvre syndrome periodontitis (48), Down's syndrome periodontitis (20), HIV-associated periodontitis (7) and acute necrotizing ulcerative gingivitis (6). Other members of the herpesvirus family can also be detected in periodontitis (8), but their association with destructive periodontal disease is not clear. Recently, herpesviruses have also been implicated in the pathogenesis of esophagitis, pneumonitis and other medical diseases previously considered to be solely of bacterial origin (15, 21, 29).

HCMV and EBV-1 are ubiquitous agents that infect individuals from diverse geographic and economic backgrounds. In most individuals, primary infection by HCMV and EBV occurs early in life and is clinically inapparent (5, 35). When clinical illness from HCMV occurs, it is usually manifested as an infectious mononucleosis–like syndrome. HCMV can also be the cause of chorioretinitis, various gastrointestinal infections, central nervous system disease and possibly some types of atherosclerosis (19, 42). The classical illness induced by EBV is infectious mononucleosis (34, 35). EBV has also been implicated in Burkitt's lymphoma

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SARS-CoV-2 Detection in Gingival Crevicular Fluid

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Abstract

Understanding the pathophysiology of the coronavirus disease 2019 (COVID-19) infection remains a significant challenge of our times. The gingival crevicular fluid being representative of systemic status and having a proven track record of detecting viruses and biomarkers forms a logical basis for evaluating the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The study aimed to assess gingival crevicular fluid (GCF) for evidence of SARS-CoV-2 in 33 patients who were deemed to be COVID-19 positive upon nasopharyngeal sampling. An attempt was also made to comparatively evaluate it with saliva in terms of its sensitivity, as a diagnostic fluid for SARS-CoV-2. GCF and saliva samples were collected from 33 COVID-19–confirmed patients. Total RNA was extracted using NucliSENS easyMAG (bioMérieux) and eluted in the elution buffer. Envelope gene (*E* gene) of SARS-CoV-2 and human RNase P gene as internal control were detected in GCF samples by using the TRUPCR SARS-CoV-2 RT qPCR kit V-2.0 (I) in an Applied Biosystems 7500 real-time machine. A significant majority of both asymptomatic and mildly symptomatic patients exhibited the presence of the novel coronavirus in their GCF samples. Considering the presence of SARS-CoV-2 RNA in the nasopharyngeal swab sampling as gold standard, the sensitivity of GCF and saliva, respectively, was 63.64% (confidence interval [CI], 45.1% to 79.60%) and 64.52% (CI, 45.37% to 80.77%). GCF was found to be comparable to saliva in terms of its sensitivity to detect SARS-CoV-2. Saliva samples tested positive in 3 of the 12 patients whose GCF tested negative, and likewise GCF tested positive for 2 of the 11 patients whose saliva tested negative on real-time reverse transcription polymerase chain reaction. The results establish GCF as a possible mode of transmission of SARS-CoV-2, which is the first such report in the literature, and also provide the first quantifiable evidence pointing toward a link between the COVID-19 infection and oral health.

Keywords: COVID-19, oral health, oral hygiene, saliva, diagnostics, periodontal

Introduction

With the coronavirus disease 2019 (COVID-19) pandemic being firmly established, understanding the pathophysiology of this novel entity has been the challenge of our times. Being a never before encountered pathogen, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has afforded no luxuries to those attempting to build knowledge in the face of this continuously mounting challenge. An essential part of improving understanding is to extrapolate what is already known. This has prompted the search for viral loads in various body fluids paralleling the presence of other viruses in these secretions. The search has entailed an assessment of viral titers in every fathomable body secretion such as cerebrospinal fluid (CSF), saliva, urine, feces, semen, breast milk, tears, and peritoneal fluid, of which samples of saliva, urine, feces, breast milk, and peritoneal fluid have demonstrated the presence of SARS-CoV-2 (Hung et al. 2003; Al Saiegh et al. 2020; Coccolini et al. 2020; Groß et al. 2020; Paoli et al. 2020; Sun et al. 2020; Xia et al. 2020). The evidence for most of these has so far been inconclusive. This, however, is true for most evidence pertaining to SARS-CoV-2, with most of the literature base being built upon a foundation of opinions, correspondence, and isolated clinical experiences. Valuable as these may be, there is a necessity to conduct proper clinical studies with standardized methodologies if we are to begin to draw some much-needed conclusions about how this virus behaves. A systematic review conducted on such meager data reveals olfactory and gustatory symptoms to be present in most patients with COVID-19, with a substantial majority of these even

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Saliva and viral infections

PAUL L. A. M. CORSTJENS, WILLIAM R. ABRAMS & DANIEL MALAMUD

Overview of viral infections

There is no single infectious route used by *all* viruses. Human viral infection and transmission can occur through multiple paths, such as fecal–oral, ingestion of contaminated food and drinks, sexual contact, exposure to infected blood, exchange of saliva or by aerosols generated by sneezing or coughing. Common examples of viruses isolated from the oral cavity include rotavirus, norovirus, HIV, hepatitis C virus, herpes simplex viruses 1 and 2, Epstein–Barr virus and influenza viruses.

Influenza and the common cold viruses are among the most frequent types of human viral infections. The common cold is generally not life threatening and usually resolves without medical intervention. As it is caused by a group of highly contagious airborne viruses for which no vaccine is available, the best protection is to avoid close proximity to individuals who are infected. By contrast, influenza results in many fatalities, particularly in the elderly and in individuals with suppressed immune systems. Annually modified influenza vaccines available in the western world were initially offered to individuals at risk but are now available to everyone. However, it should be noted that (87) 'The influenza vaccine was only 62% effective among people who did not receive influenza vaccination in the prior year. In comparison, vaccine effectiveness among those who did get influenza vaccination in the previous year was substantially lower.' Occasionally, a new influenza variant may cause a pandemic as a result of zoonosis (i.e. transmission of an animal flu virus to humans) or 'genetic recombination' (more precisely, reassortment of gene segments) of a human virus with a nonhuman form that crosses species. Well-known recent examples of these are swine flu and avian or bird flu, which is sometimes confused with the zoonotic severe acute respiratory syndrome virus (a corona virus).

Worldwide policies to reduce or eliminate the risk of epidemics have had some success, and several infectious diseases have been largely eradicated or are under control in the western world as a result of national vaccination programs. The most successful example of a human-driven eradication is that of the smallpox virus following implementation of a worldwide vaccination strategy. This approach succeeded because the smallpox virus (variola) is essentially comprised of a single strain and does not have an animal vector. The approach to measles is another example demonstrating the success of vaccines. Measles is a highly contagious infection of the respiratory system that spreads through aerosol transmission or contact with nasal and oral fluids. Effective vaccines are available and in the USA measles was declared eliminated in 2000. In 2010, at the 63rd World Health Assembly, a global goal was proposed to eliminate the disease with a target of a 95% reduction in mortality by 2015. Unfortunately, there has been a recent measles outbreak in the USA (288 cases), mostly in unvaccinated individuals (www.CDC.gov/measles/).

As a result of new vaccines and vaccination policies, and also improved medical care and development of novel drugs, worldwide infectious disease fatalities have not increased in the past two decades. However, a significant decrease worldwide can be expected only when the equivalent of western world resources become available in resource-poor areas. The global approach to eradicate polio is another example, with currently up to 80% of the world's population living in polio-free regions and a 'collaborative strategic endgame plan' in place to eradicate the last reservoirs of polio (the Global Polio Eradication Initiative). The list of viral infections and viral diseases is extensive and the eradication of one pathogen may provide a niche for another pathogen to become more virulent. Naturally acquired immunity through exposure to the pathogen is likely to provide the best protection against recurring infection.

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DISCUSSION PAPER

Is the oral cavity relevant in SARS-CoV-2 pandemic?

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Abstract
Objectives Recent scientific evidences suggest a relevant role of the oral cavity in the transmission and pathogenicity of SARS-CoV-2.
Methods A literature search was performed in PubMed, up to April 30, 2020, focusing on SARS-CoV-2, COVID-19, oral cavity, and antimicrobial agents.
Results Oral viral load of SARS-CoV-2 has been associated with the severity of COVID-19, and thus, a reduction in the oral viral load could be associated with a decrease in the severity of the condition. Similarly, a decrease in the oral viral load would diminish the amount of virus expelled and reduce the risk of transmission, since (i) during the first 10 days, the virus mainly accumulates at the nasal, oral, and pharyngeal area; (ii) the number of angiotensin-converting enzyme (ACE2) receptor is greater in the salivary glands as compared with the lungs; and (iii) salivary droplets represent the most relevant transmission route. To reduce the oral viral load, antiseptic agents may be used, although the evidence on its efficacy is indirect and weak.
Conclusions Antiseptic mouth rinses, such as those containing cetylpyridinium chloride or povidone-iodine, may be able to decrease the severity of COVID-19 by reducing oral viral load in infected subjects and decreasing the risk of transmission by limiting viral load in droplets, generated in normal life, or in aerosols, produced during dental procedures. Well-designed clinical and preclinical research must be conducted to support these hypotheses.
Clinical relevance Antiseptic mouth rinses may help in decreasing the severity of COVID-19 and in reducing the risk of transmission.

Keywords SARS-CoV-2 · COVID-19 · Antiseptic · Oral health · Transmission

COVID-2019 and oral cavity

Coronavirus 2 of severe acute respiratory syndrome (SARS-CoV-2), previously known 2019 novel corona virus (2019-nCoV), a member of the Coronaviridae family is the responsible agent of the disease referred as 2019 coronavirus disease (COVID-2019). This disease was first identified in Wuhan (China), and from there, it has spread to more than 185 countries, acquiring pandemic characteristics, with more than 2.8 million of confirmed cases and almost 0.2 million of dead, on April 25, 2020 [1].

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Most patients with COVID-19 present a mild disease, with fever, myalgia or fatigue, and dry cough as main symptoms [2]. However, almost 14% present signs and symptoms of a severe disease, requiring hospitalization and oxygen support, and 5% need to be admitted to intensive care units [3]. These severe cases usually include impairment of the function of different organs such as acute kidney injury, cardiac injury, and liver dysfunction and grave complications as severe acute respiratory syndrome (SARS), sepsis, and septic shock [4]. The risk factors associated with this severe systemic impact of COVID-19 in a small proportion of patients infected with SARS-CoV-2 have not been properly identified, although it has been suggested that the presence of other comorbidities, such hypertension, diabetes, coronary disease, aging, and obesity may play a significant role [5].

The role of the oral cavity, as the entrance to the body of SARS-CoV-2, and its possible role as protective/aggravating factor in the infectivity and in the progression of this viral infection have been controversial, although recent scientific evidences suggest a relevant role of the oral cavity and its