Review Article

University J Dent Scie 2021; Vol. 7, Issue 2

Plausible Correlation Between Sars-Cov2 and Periodontal Disease and Vice-versa: A Review.

Abstract:
Periodontitis is an inflammatory disease which affects the surrounding periodontal tissues and the primary etiological factor is the pathogenic microorganism. Apart from periodontal microbiome, various studies have shown that virome may play a role in etiopathogenesis of periodontal disease. Recently COVID-19 caused by the virus SARS COV-2, has raised a global emergency. This virus belongs to the family of Coronaviridae which is an RNA virus that created havoc worldwide. This virus has affected millions of people globally. Angiotensin converting enzyme-2 (ACE-2) has been considered the main receptor for the virus entry into target cells. Oral cavity and periodontal structures are also found to have these receptors. This fact possesses a risk as SARS CoV2 can aggravate periodontal disease as well as may increase the risk of CoV2 spread or its severity. This review will give an insight about the possible correlation between COVID and periodontal disease.

Keywords : COVID-19, Periodontal disease, ACE-2.

Key Messages : Apart from periodontal microbiome,viruses also play arole in etiopathogenesis of periodontal disease.. Recently COVID-19 caused by the virus SARS COV-2, has raised a global emergency. ACE-2 is the primary receptor for the virus entry. These receptors are also seen in periodontal structures. Therefore this review gives possible relation between COVID and periodontal disease.

Introduction:

Periodontitis is a multifactorial disease caused primarily by pathogenic microorganisms that affects the supporting structures of the teeth resulting in alveolar bone loss, pocket formation, loosening of teeth and recession. During the last few decades research has pointed out that viruses may also be involved in the pathogenesis of the periodontal diseases. Various viral pathogens have been identified which play an important role in periodontal destruction. The most commonly investigated virus which results in periodontal destruction belongs to the Herpes virus family which is a DNA virus. Various studies have also shown a relation between Cytomegalovirus and Epstein bar virus with periodontal destruction. On 30th January 2020, COVID-19 caused by the virus SARS COV-2, to be a global emergency [1]. This virus belongs to the family of Coronaviridae which is an RNA virus. So focus has increased on understanding a possible correlation between Coronaviridae group of viruses and periodontal disease and vice versa. This review gives an insight about the Coronaviridae family of viruses and also highlights about SARS CoV-2 and its possible bidirectional association with periodontal disease.

Viruses:

Viruses are the smallest known infective agents. They are obligate intracellular parasites and are perhaps the simplest form of life known. Viruses are classified into DNA and RNA viruses (Table I &II)) [2].

Access this article online

Website: www.ujds.in

Quick Response Code

DOI: https://doi.org/10.21276//ujds.2021.7.2.28

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Received : 28 May, 2021, **Published :** 31 August, 2021

How to cite this article: Bhosale, N. (2021). Plausible Correlation Between Sars-Cov2 and Periodontal Disease and Vice-versa: A Review. UNIVERSITY JOURNAL OF DENTAL SCIENCES, 7(2).: 143-149

Table 1: Types of DNA viruses

DNA VIRUSES			
FAMILY	SUBFAMILY	GENUS	COMMON MEMBERS(Species)
Poxviridae	Chordopoxvirinae	Orthopoxvirus	Variola ,Vaccinia cowpox, Monkeypox, ,Ectromelia and Rabbitpox viruses
Herpesviridae	Alphaherpesvirinae Betaherpesvirinae Gammaherpesvirinae	Simplex virus Varicellovirus Cytomegalovirus Roseolovirus Lymphocryptovirus	Herpes simplex virus types 1 and 2 Varicella –zoster virus Human Cytomegalovirus Human Herpes virus 6 Epstein-Barr virus
Adenoviridae	-	Mastadenovirus	47 serotypes of Adenovirus (h-Ad1 to h-Ad 47)
Papovaviridae	-	Papillomavirus Polyomavirus	Wart viruses Human Polyomaviruses
Hepadnaviridae	-	Orthohepadnavirus	Hepatitis B virus of man, woodchuck and other animal hepatitis viruses
Parvoviridae	-	Dependovirus Erythrovirus	Adeno associated viruses(AAV) Parvovirus B19

Table II: Types of RNA viruses

RNA VIRUSES			
FAMILY	SUB-FAMILY	GENUS	COMMON MEMBERS
Orthomyxoviridae	-	Influenzavirus A and B Influenzavirus C	Influenzavirus A and B viruses Influenza C Virus
Paramyxoviridae	Paramyxovirinae	Paramyxovirus Rubulavirus	Human parainfluenza virus types 1 and 3 Human parainfluenza virus types 2 ,4a and 4b and mumps virus
Togaviridae	-	Alphavirus Rubivirus	Eastern,Western and Venezuelan equine encephalitis viruses, Chikungunya virus. Rubella virus
Flaviviridae	-	Flavivirus Hepatitis C	Yellow fever ,Dengue HepatitisCvirus
Coronaviridae	-	Coronavirus	Coronaviruses of mammals and birds

Replication of Virus:

The genetic information necessary for viral replication is contained in the viral nucleic acid, but the biosynthetic enzymes are lacking. They replicate by taking over the biochemical machinery of the host cell and redirecting it to manufacture of virus components. [2]

The process of viral replication is divided into 6 stages [2]:

A. Adsorption: It is the first event in infection of a cell by virus i.e., attachment of the virus particle to the cell surface. This is achieved by binding of virion surface structures known as ligands to receptors on cell surface.

B. Entry into the host cells: Viruses enter the host cells by one of the mechanism; as non-enveloped virus, enveloped virus or Bacteriophages.

C. Uncoating: This process involves stripping the virus of its outer layers and capsid, so that nucleic acid is released into the cell.

D. Biosynthesis(Fig;1): This phase includes the viral nucleic acid, Capsid protein, enzymes necessary in various stages of viral synthesis, assembly and release.

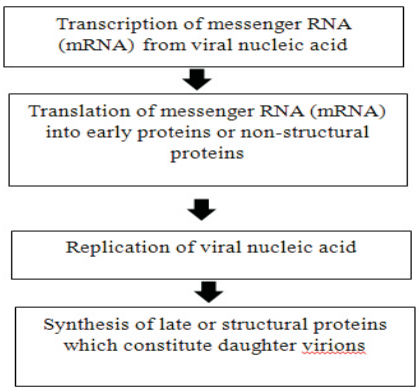

Fig I: Steps in Biosynthesis (2)

A. Virion assembly: Assembly of the various viral components into virions, occurs after the replication of the viral nucleic acid.

B. Release : Release of completed viruses is the final step in virus multiplication

Corona viridae virus:

They are large, enveloped, single-stranded RNA viruses and are the largest known RNA viruses, with genomes ranging from 25 to 32 kb and a virion of 118-136 nm in diameter. Virions are roughly spherical and are notable for the large spike (S) glycoprotein that extends16-21 nm from the virus envelope (Fig II). The family contains two subfamilies, the Coronavirinae and the Torovirinae.[3]

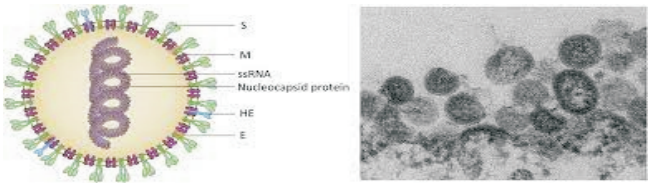

Fig II: Virion structure (subfamily Coronavirinae) (right). TEM image of MERS-CoVvirions in culture (left). From

CDC/Cynthia Goldsmith, AzaibiTamin, Ph.D. Public Health Image Library Image #17280.

The family Coronaviridae consists of subfamily Coronavirinae which includes Genus Alpha coronavirus, Genus Beta coronavirus, Genus Gamma coronavirus, The disease caused by Coronaviruses are Severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS), Feline Coronavirus and the most recently SARS CoV-2 (COVID 19).[3] A. Severe acute respiratory syndrome (SARS): SARS-CoV was detected in the human population in 2002.in China. Approximately 8000 cases were reported worldwide. According to the epidemiological studies and genetic analysis the virus was most likely transferred from bats into farm-raised Himalayan palm civets (Pagumalarvata) and then into humans. Human to human transmission was by respiratory and faecal routes. This infection causes a triphasic pattern of disease; the first phase is nonspecific with fever, cough, sore throat, and myalgia. Breathing difficulties (dyspnoea) showed up 7-14 days after appearance of the first symptoms. The second phase of the disease includes shortness of breath, fever, onset of hypoxia, and often diarrhoea. In the most serious cases, patient's progress to a third phase with development of acute respiratory distress requiring hospitalization and mechanical respiration.[3] B. Middle East Respiratory Syndrome (MERS): MERS reported over 1600 human cases with the fatality rate more than 30%. The countries that were most affected were the Arabian Peninsula. The casual transmission from person to person is very rare but most person to person transmission occurred in a hospital setting. The symptoms of MERS started initially with coughing, fever, and breathing which later on progressed to pneumonia and kidney failure. Sporadic cases of MERS still continue to be reported. [3] C.SARS CoV-2 (COVID 19): On March 11, 2020 World Health Organization (WHO) identified Coronavirus disease 2019 (COVID-2019) which is caused by a novel coronavirus known as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as pandemic[4]. This virus was first identified in the respiratory tract of patients with pneumonia in Wuhan, Hubei China, in December 2019 which was then indicated as a newly identified Beta-coronavirus (CoV) [5, 6].

Structure and Entry Of Coronavirus:

SARS-CoV2 is a novel Beta coronavirus which consists of four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocaspid (N) protein, and also several accessory proteins [7]. The spike or S glycoprotein is a transmembrane protein with a molecular weight of about 150 kDa which is found in the outer portion of the virus. It forms homotrimers protruding in the viral surface and facilitates binding of envelope viruses to host cells by getting attracted towards angiotensin-converting enzyme 2 (ACE2) mostly expressed in lower respiratory tract cells.

The nucleocaspid known as N protein, is the structural component of CoV. It is structurally bound to the nucleic acid material of the virus and thus N protein is responsible for the viral genome, the viral replication cycle and the cellular response of host cells to viral infections [8, 9].The membrane or M Protein, is the most structurally structured protein which plays a role in determining the shape of the virus envelope. The last component is the envelope or E protein which is the smallest protein in the SARS CoV structure that helps in the production and maturation of this virus [8]. The primary entry of this virus is believed to be through projected droplets leading tothe first contact and colonization of cells in the oral cavity, nose or eyes [6]. People positive for this virus develop variable symptoms in mild form (fever, cough, headache, anosmia, ageusia etc.). In moderate to severe cases, respiratory failure occurred and in some cases it can lead to intensive care unit hospitalization and eventually death [10]. In supporting the process of entry of the virus into the host cell, SARSCoV2 binds to the ACE2 receiver which is highly expressed in the lower respiratory tract, such as type II alveolar cells (AT2) of the lungs, upper esophagus and stratified epithelial cells, and other cells (such as absorptive enterocytes from the ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells) [11]. Therefore, patients who are infected with this virus not only experience respiratory problems such as pneumonia leading to Acute Respiratory Distress Syndrome (ARDS), but also experience disorders of heart, kidneys, and digestive tract.

Role of ACE2 In Inflammation:

ACE2 is an important component of the RAS (Renin angiotensin system) and it is the regulator of the RAS system. It functions by modulating the damaging actions of Ang II and At1, (angiotensin receptor type 1), thereby decreasing the inflammatory response[12]. Whereas ACE increases the production of AngII which plays a key role in activation of protein kinases and recruitment of inflammatory cells and synthesis and release of cytokines and chemokine's[13,14]. Therefore ACE has a destructive function. ACE2 regulation is achieved by several mechanism.It acts as a mediator in the conversion of Ang I to Angiotensin 1–9 (Ang1–9) instead of Ang II, thereby producing an anti-inflammatory response. ACE2 also acts directly on Ang II and converts it to the vasodilator Ang1–7, thus it increases the production of Ang1–7 at the expense of Ang II. Ang1–7 mediates itsvasodilatory and antiproliferative effects via MasR [15,16].Other protective effects of the ACE2/Ang1–7/MasR axis include reductionin the release of pro-inflammatory cytokines [17].

ACE 2, Periodontal Tissues and Cov 2

Oral expression of ACE2:

ACE2 is an important component of the RAS and is linked to the entry of SARS-CoV-2 into target cells through endocytosis and internalization of ACE2.Angiotensin converting enzyme-2 (ACE-2) has been found to be expressed by various types of cells such as pulmonary cells, nasopharyngeal cells, salivary gland cells etc. Recently published data indicate that cells from the oral cavity (Dorsum of tongue, Sulcular epithelium) highly express ACE-2 in a comparable manner to that of lung cells [18]. Sahni and Gupta (2020) [19] have also confirmed the expression of ACE-2, in gingival and periodontal ligament fibroblasts, in rat and human tissues. In cases of active periodontal disease there is increase of Furin and Cathepsin L proteases which enable SARSCoV 2 to bind to ACE 2 receptors and facilitateendosomal fusion in host cells. [20]

Periodontal Pocket as a Niche for Sars Cov 2:

Due to presence of ACE 2, periodontal pocket can act as a reservoir for the SARSCoV-2 viral infection as it could also provide a favorable environment for viral replication and survival. There are various studies which have shown detection of viruses in the periodontal pocket[21]. There are two possible sources of SARS CoV2 infection of periodontal pocket and tissues. First is direct infection coming from oral cavity[18, 19].Secondfrom the circulating peripheral blood mononuclear cells from SARS CoV2 infected patients because this SARScorona virus replicates in mononuclear cells[22]. As periodontitis shows continuous inflammatory response, this could attract these infected peripheral mononuclear cells to the pocket area through systemic circulation[22]. Therefore this directs to the fact that periodontal pockets are compatible environments for viral infection and survival. It can further be stated that these pocket viruses due to flushing action of GCF may cause the viruses to mix with saliva which may further increase the risk of spread of infection through saliva droplets.[23] It can also be suggested due to this fact that, aerosol generating procedures in periodontics may amplify viromes aerosol concentration in the air and on inanimate surfaces which can increase the danger of cross infection.[24]Thus, periodontal pocket, a niche for viral growth can be considered a suitable site for sample collection for COVID -19 testing.

Role of ACE2 in SARS Cov 2:

As already stated, ACE2 is a primary receptor for SARSCoV-2 infection [25]. The Viral replication leads the immune system to down regulate ACE2 expression at the cell surface (through its internalization) and thus decreases the degradation of Ang II, leading to an increase in ACE and Ang II which could exacerbate the inflammatory pattern of the SARS-CoV-2 infection.[26-30]. Ang II favours the recruitment of infiltrating inflammatory cells into tissues by stimulating the production of specific cytokines/chemokine such as the potent monocyte chemoattractant protein 1 (MCP-1). Other cytokines involved in the onset and progression of the viral inflammatory condition are tumour necrosis factor alpha (TNF-a), interleukin-6 (IL-6), and interleukin-1 beta

(IL-1), inducing apoptosis of endothelial cells and the activation of macrophages in the inflamed tissue or organ. [31] This helps us understand the hyper inflammatory response (Cytokine storm) in CoV2 infected patients [32].

Role of ACE2 and Cov 2 in Progression of Periodontal Disaese

As previously mentioned, various studies have shown the presence of ACE2 and consequently of the RAS (Renin–angiotensin system) system, mainly in the cells associated with the periodontal structure [30]. As bacteria are involved in facilitating the initiation of an inflammatory response inside the periodontal pocket, during a SARSCoV-2 coinfection, the complex formed between the virus and ACE2 proteins leads to reduction in ACE2 levels in infected tissues [33], and this might increase the expression of cytokines, with the consequent activation of the osteoprotegerin (OPG) – the receptor for RANK-Ligand (RANK)–RANKL axis, stimulating osteoclast function.[34] Thus periodontal pattern might be exacerbated due to the down regulation of ACE2 and an increase in ACE and Ang II, with the consequent involvement of several pro-inflammatory cytokines such as IL-6, IL-7, IL-2, TNF-a, IL-1and MCP-1.This plays a crucial role in progression of periodontal disease .[35]

Role of Periodontal Disaese in Increasing The Severity of Cov 2:

As discussed above, it is clear that there is increase in inflammatory markers (exaggerated systemic inflammation) in CoV 2 patients. Periodontal disease is also an inflammatory condition where the inflammatory mediators are disseminated to distant body sites through circulatory system and oral gut access.This leads to increase in serum inflammatory markers . However it has a different initiation pathway related to biofilm and bacteria [19]. Periodontitis thus may increase the CoV-19 symptoms with increased blood levels of biomarkers worsening the disease outcomes leading to higher risk of ICU admission, need for assisted ventilation and death of COVID-19 patients.

Conclusion:

Periodontal pockets are peculiar isolated environments. It presents proper biological dynamics, with two-way interactions within the oral cavity on one hand and the systemic circulatory system via gingival blood vessels on the other.[36] It is becoming more widely accepted that besides the bacterial challenge, viruses from periodontal pocket could infect distant organs and hence generate focal infections [37]. The presence of ACE2 in both SARS CoV 2 target tissues and periodontal tissues, points out towards a possible correlation between SARS-CoV2 and periodontitis. This can cause down regulation of this enzyme in periodontal tissues too, which further causes activation of several cytokines. Overexpression of this inflammatory response in both the diseases can complicate the disease severity. In order to tackle this COVID 19 pandemic, it is important to understand the hidden viromereservoirs to reduce its spread. This will greatly helpin carrying out preventive and safety measures. This review has tried to highlight that periodontal pocket could be a favourable niche for the virus and thus it may increase the COVID-19 symptoms with increased blood levels of biomarkers worsening the disease outcomes. Therefore periodontal preventive measure could beconsidered a parameter of care in the clinical management of COVID positive patients, aiming at reducing the viral reservoir in periodontal pockets. However these research areas need to be explored further to increase the scope of survival in this pandemic.

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