

# COVID-19 PANDEMIC AND PERSPECTIVE CONVERGENCE WITH PERIODONTAL DISEASES

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### ABSTRACT

This review aim to discuss the important components of Coronavirus Disease (COVID-19) and possible correlations, interactions with oral/periodontal structures. With the beginning of the announcement of the transformation of COVID-19 from an epidemic into a pandemic, it was necessary to realize the injury of several million people infected with this disease and others will become infected soon and its impact on public health as well as the adverse effect of chronic diseases and their causes for the spread of COVID-19. Chronic periodontal diseases are one of the most widespread diseases around the globe and one of their supposed causes is the presence of many microbial plaques, including bacteria and viruses. Presence of coronavirus receptors on the cells of the oral mucosa, and cells of the periodontal pockets, may give a way to adhere the virus and spread inside the body through the periodontium. SARS-CoV-2 virus was found in some saliva samples. A conceivable relevance between periodontitis and COVID-19 has been hypothesized. Defense against COVID-19 in dental clinical consist of three ascending levels. It is advised to utilize a mouth rinse against SARS-CoV-2. At end of this review, oral health providers and periodontists will gain essential knowledge to the successful confrontation against the Coronavirus Disease (COVID-19).

**Keywords:** SARS-CoV-2, COVID-19, periodontal diseases, Pandemic.

## Introduction

In association with specific bacterial pathogens like red complex bacteria, etiopathogenesis of periodontal diseases may include many viruses as active herpesviruses, and it associated with unbalanced immune restraint including pro/anti-inflammatory cytokines (Slots 2015). Some viruses like Herpesviruses act by infect or alter periodontium components and immune cells within periodontium and thereby decrease efficiency of periodontal tissues to overcome bacterial overloads (Contreras et al., 2014).

Synergistic effects of viruses enhance microbial replication or infectivity of another microbes. The human immunodeficiency virus (HIV) with specific Epstein-Barr virus (EBV) progenies show growing replication within CD-4 cells (Zhang et al. 1997). with assisting of herpes simplex virus (HSV)-1, HIV can enter keratinocytes, which are commonly avoider to invasion as these cells don't have the CD4 molecule (Heng et al., 1994).

The aftermost evidence for a possible microbial correlation between human herpesvirus 4 (EBV) and some periodontopathogenic bacteria in periodontal etiopathogenesis was reported in observations suggested that butyric acid by-product of periodontal bacteria have the capacity to target Epstein-Barr virus reactivation in the periodontium of EBV-infected individuals and control switching from latency to reactivation considered as an initial step in EBV infection (Imai & Ogata, 2020). Redondoviridae, a family of tiny, annular DNA viruses newly located in metagenomic series map, can assist and persist the inflammation status associated with periodontal diseases and contribute to disease aggression via their infection and replication (Abbas et al., 2019) (figure.1).

Acute virally infected patients are showing high accretion of bacterial invasions. The study of influenza outbreaks in humans gives the clearest and strongest clue of the effect of viral infections on the spread of bacterial diseases. Streptococcus pneumonia and Staphylococcus aureus bacterial super infections result in altitude of morbidity and mortality during influenza epidemics (Abramson & Mills, 1988) (figure.1).

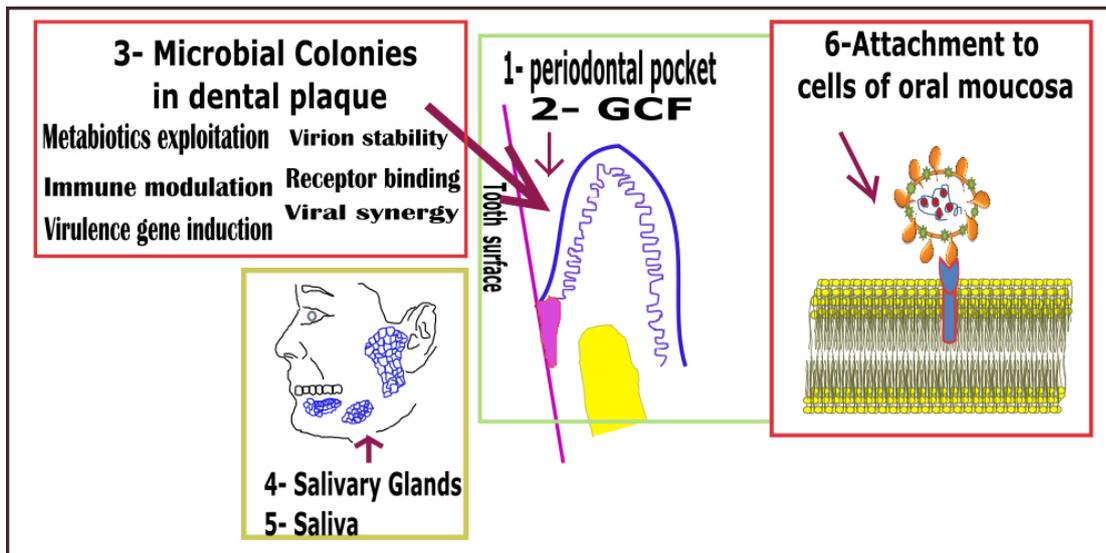


Figure.1 showing potential sites of coronavirus (SARS-CoV-2) in oral cavity and possible polymicrobial interactions between bacteria and viruses which leading to synergism, stability, coinfection, bacterial superinfection. Abbreviations; (GCF, Gingival Crevicular Fluid),

By the beginning of 2020, “World Health Organization” (WHO) termed the virus severe respiratory syndrome-coronavirus-2 (SARS-COV-2), constructing it as major outrage for acute respiratory distress syndrome (ARDS), and the malady was termed “coronavirus disease 2019 (COVID-19)”. by the time, a state of COVID-19 became pandemic, and it was known as a public health contingency of international disquiet (J. Wong et al., 2020;Khongsai et al., 2020).

Coronaviruses are determined as the massive group of viruses, which being owned by the *Nidovirales* order, including *Coronaviridae* (alpha, beta, gamma, and delta), *Arteriviridae*, and *Roniviridae* families. Their main structures are coated, undivided positive-sense RNA. Digestive and respiratory sickness in animals, and fatal respiratory distress in persons can be caused as manifestations of coronavirus infection (Fehr & Perlman, 2015). As members of *Coronaviridae* family, severe acute respiratory syndrome coronavirus (SARS-CoV), specified in 2002, and the Middle East respiratory syndrome coronavirus (MERS-CoV), specified in 2012 (Wax & Christian, 2020). Newly incoming betacoronavirus (SARS-CoV-2) has resemblance to coronavirus species habituated in bats and pangolins, supporting the zoonotic essence of this recent wandering viral-mediated disease (Zhou et al., 2020; Wahba et al., 2020;PANDEY et al., 2020)

The components of SARS-COV-2 structure include a nucleocapsid(N) with a single stranded RNA core, a spherical lipoprotein envelope(E) and matrix protein(M) with protruding spike shape proteins (S), which are adhering to specific receptors of the host cells to be infected (Gorbalenya et al., 2020) (figure.2). SARS-COV-2 needs incubation period from 1 to 14 days to be contagious in its latency interval (Pereira et al., 2020). Its replication cycle was correlated with the harmful impacts, appearing as cellular lesions and increased cell death (Earar et al. 2020). Viruses have stealth capacity to escape

from host immune defense and to inactivate the host interferon system which interfering with pattern recognition receptors (PRRs) alerting routes to evade host defense (Kindler et al., 2016).

The SARS-CoV N proteins inhibit *retinoic-acid inducible gene 1* (RIG-I) conjunction with ubiquitin and thus decrease the emission of type I IFN (Interferon) (Hu et al., 2017). M proteins restrains *TNFR-associated factor/ TANK-binding kinase* (TRAF3/ TBK1) complex formation and blocks activation of *Interferon regulatory factor 3 / Interferon regulatory factor 7* (IRF3/IRF7) transcription factors (Siu et al., 2009). The SARS-CoV Nonstructural Protein (nsp1) prohibits host mRNA translation and initiates host mRNA degradation [(Tanaka et al., 2012;Huang et al., 2011).

Three routes of the SARS-CoV transmission have been found. Firstly, contact transmission: when someone touches an infected object and subsequently touches his mouth, nose or eyes. Secondly, Droplets transmission: when the droplets generated by cough and sneezes are ingested or inhaled. Finally, Airborne transmission: when air contaminated by droplets, creating aerosols that results in infection if inbreathed (Adhikari et al., 2020; Harte, 2010) . Fecal-oral transmission is considered possible as well (Zhang et al., 2020).

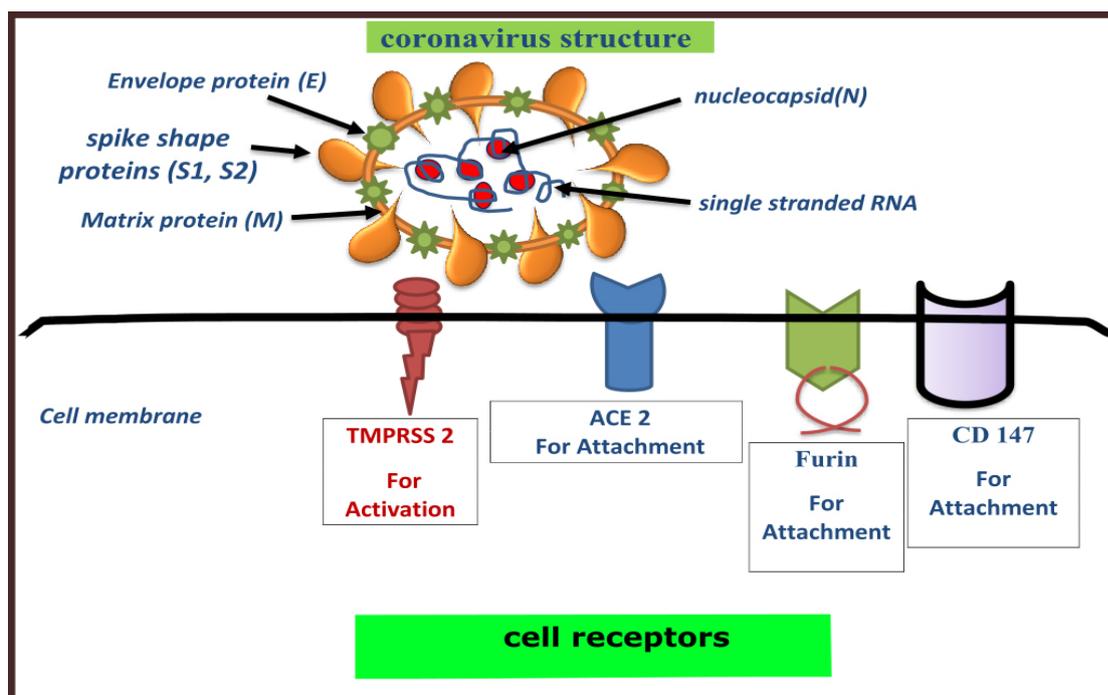


Figure 2. Showing fictional form for coronavirus (SARS-CoV-2) and its structures; also, possible host cell membrane receptors.

During the massive spread of pandemic COVID-19, Attention to use tele-communication or tele-dentistry prior periodontal management to estimate the patient status also to diminish the risk of virus spread, quizzing if sickly person has common cold/ bronchitis symptoms and have went abroad national or internationally. In this significance, the treating team members necessarily use clinical judgment remotely and every possible precaution must be taken to prevent disease transmission (Pereira et al., 2020). In dental clinics, many necessary and successive measures must be taken during the rapid spread of the COVID-19 epidemic as follows; waiting room for one patient only , strict adherence to the infection control procedures, ideal steps of wearing and taking off all Personal Protective Equipment (PPE), including protection tools for all exposed skin, eyes, mouth, face and hands (Pereira et al., 2020). Before beginning of treatment, a patient rinsing with 1% or 1.5% hydrogen peroxide or 0.2% povidone also he should wear goggles and apron until ending of procedure (Pereira et al., 2020). Aerosols generation must be limited through using manual instruments and high-suction for saliva during the periodontal therapy and avoiding 3-in-1 chip syringe (Kharma et al., 2015).

### ***SARS-CoV-2 colonization into periodontal pockets***

A Periodontal pocket is a unique isolated site in the human body, presenting qualified biotic dynamics, with bidirectional linkage with the oral environment via periodontal crevicular fluid exudate on one direction and systemic circulation via gingival peripheral blood capillary networks on the other hand (Badran et al., 2020). Initial viral infection of periodontal tissues have occurred through direct contact of gingival epithelial cells exposed to the oral cavity with virus, or virus wandering and entrance via the blood supply or virally affected defense cells in the periodontal inflammatory transudate (C. S. Miller, 2014). The viral observations in periodontal pocket, have been affirmed such as Herpes simplex virus (HSV) type 1, type 4 (EBV) and type 5(HCMV) (Cappuyns et al., 2005).

The main gate of Coronavirus is proposed to be by emerged droplets results in a former nexus and habitation of cells in the oral environment (Lo Giudice, 2020). The main receptors to this virus are Angiotensin converting enzyme-2 (ACE-2) (Zou et al., 2020) , Furin (proprotein convertase) (Izaguirre, 2019) and Cluster of Differentiation 147 (CD 147) (K. Wang et al., 2020) ; these receptors were highly expressed in fibroblasts of periodontium ligaments (Santos et al., 2015) , in oral epithelial cells (Zhong et al., 2020) and the sulcular epithelium of periodontal pocket (Feldman et al., 2011).

Coronavirus' conjugation to membrane receptors, are suitable with an assumed attachment to periodontal pocket. This could encompass the sulcular/gingival epithelial lining also the gingival/periodontal fibroblasts (Badran et al., 2020) . By different pathway, SARS-CoV can invade and reproduce in mononuclear cells (infecting T-Lymphocytes) but for a short span (X. Wang et al., 2020). Also, the invasion of endothelial cells by SARS-CoV-2 seems conceivable (Varga et al., 2020). It was hypothesized that periodontal pocket could represent a repository of SARS-CoV-2 depending on harmonious and feasible surveillances (Badran et al., 2020).

### ***Blatant pandemic COVID-19 and calm pandemic periodontitis***

One of pathophysiological mechanisms of COVID-19 was introduced to be correlated to a 'cytokine storm' which appearing as supreme serum levels of proinflammatory interleukins. clinical studies in COVID-19 patients showed that manifestations of the cytokine storm matched up raised TH17 pathway (Wu & Yang, 2020). Periodontal disease has a sophisticated interlace pathophysiology with increased affirmations of immunological participations; demonstrating that patients suffering from periodontal disease, having increased aggregate of Interleukin-17 (IL-17) in the serum as well as rise IL-17 output cells in gingival tissue (Graves, 2008).

A probable consortium between periodontal diseases and COVID-19 related detrimental consequences has been hypothesized. Future and present recognition of this correlation emphasizes the significance of maintaining periodontal conditions with continuous screening and the importance of keeping exacting oral hygiene in the COVID-19 interval and beyond. This probable association also tip across the potency of the existence of periodontal disease as catalyzer towards COVID-19 related detrimental effects (Sahni & Gupta, 2020).

### ***Virtual existence of SARS-CoV-2 in saliva during periodontal diseases***

The salivaomics motif which constituting from genomics, transcriptomics, proteomics, metabonomics and microRNA (miRNA) screening was proposed by **Wong** in 2012 to appear from nowhere to existence ( Wong, 2012;Santosh et al., 2020) . Many salivary mediators have been used for the scientific periodontal disease's assessment. Porphyromonas gingivalis salivary kit which is depended on an enzyme-linked immunosorbent assay (ELISA) has been introduced and endued rapid results within 90 seconds with high sensitivity and a specificity (O'Brien-Simpson et al., 2015).

As periodontal diseases can be associated with more than 70 genes (Karimbux et al., 2012), salivary genomics represent recent appealing way for the periodontal diagnosis. After analyzing salivary DNA, it was legitimized that IL-6 genetic mutations are one of considerable hazards for chronic periodontitis (Song et al., 2013).

Recently, viral infections identification by salivary biomarkers, such as viral DNA, RNA, antigens and antibodies was broadly used. Moreover, saliva considered to be more sensitive than serum in the assessment of human Herpesvirus-6 or human cytomegalovirus (Nefzi et al., 2015).For detecting the hepatitis C virus, OraQuick® hepatitis C virus rapid antibody test was used via a saliva samples (Parisi et al., 2014).

COVID-19 disease is very prevalent and super-contagious even to those who have all the means of protection and precautions from members of medical teams, especially at the beginning of diagnosis and diagnostic sampling via nasopharyngeal or oropharyngeal specimens, as a result of close proximity to potentially diseased individuals. In patients with condition such as thrombocytopenia,

nasopharyngeal or oropharyngeal swabs could result in discomfort and provoke bleeding (Chan et al., 2020). In Hong Kong Public Health Laboratory Services Branch, Saliva from twelve confirmed COVID-19 patients was gathered and submitted to nucleic acid extraction and real-time reverse transcription-quantitative polymerase chain reaction. Virus was detected in 91.7% of the initial saliva samples. In 33 recovered patients, both nasopharyngeal and saliva specimens tested negative for COVID-19 (To et al., 2020).

Extraction of viral RNA from salivary fluid was a potent gateway for COVID-19 diagnosis and has the same fulfillment to the advisable swab-based collection specimens. with the universal insufficiency of swabs for diagnosis and huge increased COVID-19 patients, Salivary swabbing will be useful, and will be dimming the demand of health care specialists to round up samples (Anjum, 2020).

Potential diagnostic and prognostic biomarkers for COVID-19 disease, could be including salivary ELISA of antibodies against SARS-CoV-2, SARS-CoV-2 double-membrane extracellular vesicles (EVs) isolation, anti-SARS-CoV-2 surface proteins, viral titers load, CD4+/CD8+ T cells derived EVs, and pro-inflammatory cytokines. Indeed, an ideal indoor saliva test would be a nonreturnable ready device used by patients, avoiding contact to a prospect environmental virus infection hazard (Han & Ivanovski 2020).

#### ***Potential relevance between COVID-19 and periodontal diseases***

Gingiva that possesses angiotensin-converting enzyme 2 (ACE2) sensors would be given a conceivable track for SARS-coronavirus-2 entrance (Xu et al., 2020) (Balaji et al., 2020). In chronic periodontitis, gingival cells have established much amount of osteopontin, which resulting in elevated the protease furin level (Sharma & Pradeep, 2007; Kumar et al., 2010) . Besides furin, cathepsin L level is also heightened (Trabandt et al. 1995).

By assistance of furin and cathepsin, SARS-coronavirus-2 enable to invade the host cells. furin divides the S protein of the virus into S1 and S2 subunits (Zhong et al., 2020) (Hoffmann et al., 2020), then S1 subunit coheres to the angiotensin-converting enzyme 2 (ACE2) located at cell surfaces (Xia et al., 2020). then final fusion occurs via two ways, cysteine proteases cathepsin B/L participation for endosomal fusion or serine protease participation for plasma membrane fusion (Xia et al., 2020). it can be assumed that the massive protease amount in chronic periodontitis could imaginably maximize endangering of an oral mediated SARS COV-2 infection (Xu et al., 2020).

### ***Periodontal diseases as reflex of general health on COVID-19***

Reported hospital-acquired pneumonia complications in periodontally diseased patients are more likely to be developed because respiratory pathogens, including *Chlamydia pneumoniae* were hiding in oral cavity (Almeida-da-Silva et al., 2019; Scannapieco, 1999, 2006).

Adequacy of oral microbes to aggravate lung contagions may be explained; via (1) entrance of oral microbes inside the lower respiratory tract, predominantly in debilitating patients (2) changes of mucosal cells throughout the length of the respiratory system by actions of salivary enzymes, which thereby favoring pathogens habitation (3) pro-inflammatory cytokines discharge through periodontal diseases, which enhancing coalescence to respiratory epithelium and settlement by respiratory microbes (Gomes-Filho et al., 2010; Varanat et al., 2017).

Oral status amelioration and refined regular periodontal interest diminish the succession or initiation of respiratory diseases, seriously in the senescent age and very ill patients (Azarpazhooh & Leake, 2006). This population is also at extreme hazard for incubating critical complications concerned to COVID-19 (Boccardi et al., 2020; Swiss, 2020). Ameliorative periodontal condition in people of any age will diminish their endangering of developing any systemic diseases and this may eliminate the ailment of COVID-19 (Botros et al., 2020).

Massive effects of COVID-19 on oral/periodontal conditions appear to be multi-directional, immune-related and supposedly indirect, expressed by several pathways, representing the pathological severity of coronavirus invasion/ stealth via mucosal surfaces (Dziedzic & Wojtyczka, 2020).

### ***Periodontal treatment and COVID-19***

Aerosols with contaminated saliva that generated by any dental procedure, can seriously elevate airborne contamination with microbes (Micik et al., 1971). Aerosols are defined as tiny diameter airborne particles with lesser 50-micron which persisting as suspensor for extended time and increase incidence of circumferential dirtiness and gets pathway into respiratory system. Beside aerosols, airborne matters with oversized than 50-micron diameter which too large to persist as suspensor in air for protracted periods, are known as splatters. Splatters are considered as droplets get out vigorously in a defamatory way like a missile until they contact a subject (Harrel & Molinari, 2004; Miller et al., 1971).

With talking, cough or sneeze, scattered virus can sustain for a longer interval as suspensor in surrounding area and may be prevailed via breathing in or communicate with infectious individuals. In 25-28 Celsius degrees, SARS-CoV-2 sticks on surfaces (inanimate flatness) across nine days, but its vitality is determined by the nature of the surfaces. It still infectious for several hours, 2-3 days, 5 days and more than 5 days in Aluminum and Copper, stainless steel and plastic, ceramics, and paper and glass respectively (Kampf et al., 2020). Selected aerosol paradigms showed that virion integrity can reach up to 16 hours pended in air under scanning electron microscope (Fears et al., 2020).

The mechanism of defense against COVID-19 in dental clinical consist of three levels. The primary level is private preservative kit such as gloves, eyeglasses and masks. The secondary level is oral rinsing with antiseptics and the tripartite level is the use of high-speed suction and adjunctive high efficiency particulate air (HEPA) filters (Bauchner et al., 2020). By contact time fifteen second, 0.25% to 0.5% povidone-iodine (PVP-I) showed prompt viricidal activity against SARS-CoV-2 ('coronavirus') to lessen the danger of propagation of the infection in the practical field. Therefore, the 10% (PVP-I) antiseptic formula should be diluted by 1:20, employing mixture of 0.5 cubic centimeter of 10% povidone iodine and 9.5 cubic centimeter of sterile water for single use at 0.5% povidone iodine concentration (Bidra et al., 2020).

Oxidizing agents such as citrox (Flavonoids as coronaviral chymotrypsin-like protease inhibitors) is used as mouth wash to constrict the virus's tonnage, encompassing potential SARS-CoV-2 transit. These oxidizing mouth rinses that comprise cyclodextrins combined with citrox could supply beneficial adjunctive periodontal therapy. Locally administered delivery systems that containing cyclodextrins combined with citrox or 0.5% povidone iodine, could diminish the SARS-CoV-2 virus's tonnage and minify the nasopharyngeal microbes, through coating aerosol and droplets throughout its rush from mouth (Carrouel et al., 2020).

Currently, the effects of COVID-19 around our planet are worsening continuously (kassaw & Pandey, 2020). Medical and scientific research community learns more about COVID-19 with more blinded, randomized clinical trials will be performed. More future knowledge about novel coronavirus pathogenesis and its effect on periodontal tissue, microbiome interactions and possible genome/epigenome will open horizons in the relationship between COVID-19 and periodontal diseases.

## Conclusion

As coronavirus was detected in saliva and epithelial cells of periodontal pocket have receptors to coronavirus attachment, this review concluded that there is close convergence between periodontal diseases and COVID-19.

## Conflicts of Interest:

The authors declare no conflicts of interest.

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