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EXPLORING PERIODONTAL HEALTH IN THE ERA OF COVID-19- A Review

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Abstract

The coronavirus disease 2019 (COVID-19) is mostly a mild condition, however, in some patients, it could progress into a severe and even fatal disease. Recent studies have shown that COVID-19 infection and severity could be associated with the presence of periodontitis, one of the most prevalent chronic diseases. This association could be explained by the fact that periodontitis and COVID-19 share some common risk factors. possible explanation could be the systemic inflammation and the aspiration of periodontopathogens seen in patients with periodontitis, which could have a synergism with the virus or compromise the reaction of the body against COVID-19. This review explores the nature of these associations, the evidence behind them, and their implications.

Keywords: Periodontal health, SARS associated covid-2

INTRODUCTION:

The coronavirus disease 2019 (Covid-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a pandemic by the World Health Organization. Being highly transmissible, the coronavirus disease has spread fast all over the world.[1]

In general, studies on Covid-19 symptoms and signs indicate as the most common headache (70.3%), loss of smell (70.2%), nasal obstruction (67.8%), cough (63.2%), asthenia (63.3%), myalgia (62.5%), rhinorrhoea (60.1%), gustatory dysfunction (54.2%), sore throat (52.9%) and fever (45.4%).[1] Okui T et al 2021 [2] states oral manifestations have been also observed in patients with Covid-19. The most frequently observed oral symptoms were dysgeusia, blisters, ulcerations and desquamative gingivitis. Within the oral cavity, the palate and tongue are the sites most commonly affected by COVID-19, followed by the gums However, growing evidence suggests that oral cavity may not only be a site of the clinical manifestations of SARS-CoV-2 infection but also can play a possible role in the virus entry and transmission.[2] Periodontitis and coronavirus disease are serious health risks that threats human life, disrupt social order, and put a heavy financial strain on the world's healthcare system.

This narrative review discusses potential connections of SARS-CoV-2 infection, Covid-19 and periodontal tissues in health and diseases as well as a likely role of periodontal healthcare in the virus spread.

Keywords: periodontal health, SARS associated covid-2,Inflammatory mediators.

DISCUSSION:

EFFECT OF PERIODONTAL HEALTH ON COVID 19:

Covid results in exacerbated immune response resulting in release of proinflammatory cytokines such as IL-6, IL-10, IL-2, IL-17 into the peripheral blood stream, similarly periodontitis also involves in release of proinflammatory cytokines and pathogens into bloodstream resulting in low grade endotoxemia and systemic inflammation (Henry b et al., 2021)[3]. Studies have shown various associations between covid and periodontitis for example, in a study have shown that CRP a keybiomarker of covid is found to be increased in covid 19 patients with increased probing depth and attachment loss with radiographic periodontal bone loss.(Luo XH,2021 & Marouf,2021)[4,5]These associations may be correlated to common immune pathways which are shared by periodontitis and Covid such as the nuclear factor kappa B (NF-κB) pathway and NLRP3/IL-1β and the IL-6 signaling pathways.(Gupta S,2022 & Liu T,2017)[6,7].Oral cavity is important pool for all respiratory

pathogens which has been increasingly debated over recent decades.A considerable number of hypothesis have sought to Zheng M et al., 2021 have explained the possible role of oral bacteria in the pathogenesis of respiratory diseases, and some clinical and epidemiological studies have found results favoring such an association.[8] Different mechanisms have explained the capability of pathogens present in oral cavity, aggravate infection in lungs, which includes aspiration of pathogens present in oral cavity towards the lower respiratory tract, more commonly among the high risk persons.(Azarphooh A,2006 & Leake JL,2006)[9].Alteration of surface along the mucosa of respiratory tract through salivary enzymes, that leads to the pathogen colonization, and release of pro-inflammatory cytokines (IL)-6, IL-10,IL-2 and IL-17 throughout periodontitis condition, that further encourages attachment to the epithelium of lung and respiratory pathogens colonization [10]. Enhancing the oral hygiene helps to declination of colonization along oropharyngeal region and reduces the complication of respiratory system. It has been observed that better hygiene on oral cavity and good care of oral health leads to declination on development of respiratory illness, which is more significantly in the older individuals and the patients admitted in ICU [8]. Aged individuals and person of any age who is experiencing severe medical conditions like heart conditions, diabetes, chronic lung disease or renal disease are at excessive risk of getting serious disorder because of SARS-CoV-2 condition.(Varanat M et al., 2017)[11].Nevertheless, substandard oral health status inclines the possibility of expanding the medical conditions like COVID 19. Consequently, enhancing the oral health status of individuals of any age group, by declining their possibility of getting any non-oral systemic conditions, would lower the rate of spread of COVID-19.[12]

Periodontal structures are possible SARS associated covid-2 infection sites:

Clinical manifestations of Covid-19 such as ulcers, vesicles, vesicular bleeding, necrotizing gingivitis, desquamative gingivitis, which have been reported to involve periodontal structures/mucosa remain unclear to be directly associated with SARS-CoV-2 infection. (Botros N,2020 & Patel J,2020)[13,14].These symptoms are rather ascribed to immune dysfunction associated with SARS-CoV-2 infection, superinfection with other microorganisms and disease-related emotional stress[13]. Long-term inflammatory process observed in Covid-19 patients may produce pathological responses in periodontal tissues leading to fibrinogen degradation and triggering coagulation cascade.(Gofur N et al., 2020)[15]. SARS-CoV-2 infection also involves changes in the bacterial flora, with increased population of Prevotella intermedia, which may trigger or worsen periodontal disease.(Chen L,2020 & Haran JP,2021)[16][17].

SARS associated covid-2 penetrates cells in oral cavity by two pathways: One through the Host cell membrane peptidases or less efficiently via endocytosis. Infection begins when the virus Spike protein (S) chemical reactions with the host cell's angiotensin-enzyme (The enzyme ACE2) on its membrane. Furin divides the spike protein into S1 and S2 subunits.

Further cleavage of S2 by transmembrane serine protease 2 (TMPRSS2), a host cell-derived protease, exposes the fusion peptide, allowing the virus to merge with the host cell's membrane and thereafter invade the cell.[18] Mayi BS et al.,2021 suggests that neuropilin-1 (NRP-1) may act as an entry factor, boosting infection with SARS associated covid-2.[18] Various tissue-specific proteases, which are TMPRSS4 and TMPRSS11D, as well as endosomal proteases (CTSB, CTSL, and BSG), can all participate in cell entry. (Singh M et 2020)[19]

The SARS associated covid-2 replication cycle: During the endosomal entering pathway, the spike protein comes into contact to ACE2, which causes the virus to be internalized. Within the endosome, cathepsin L splits the protein known as spike into S1 and S2, allowing the capsid of the virus to merge with the endosomal membrane and unleash its genome. ACE2 and transmembrane serine protease 2 play important roles in infection with SARS associated covid-2 , both during entry and transmission. Several molecular techniques have confirmed the presence of SARS associated covid-2 entrance and transmission elements in gingival tissue.(Sungnak W et al.,2020)[20]

There is growing evidence that the virus can directly infect and replicate in oral structures, that is, including the periodontal tissues. (Brandini DA,2021 & Huang N,2021)[21,22] Studies states that Furin, TMPRSS2, and ACE2 which are potential entry routes are expressed in the periodontal pocket epithelium and sulcular epithelium of gingival epithelial cells[21,22].A single-cell RNA in situ hybridization and immunofluorescence microscopy analysis of healthy gingival biopsies demonstrated ACE2 and proteases (TMPRSS2, TMPRSS4 and TMPRSS11D) expression in the gingival epithelium.[19] Gingival keratinocytes were also evidenced to express ACE2 and TMPRSS2 as well as endosomal proteases CTSB and CTSL. [19]The expression levels of SARS-CoV-2 entry factors were similar to the nasal and intestinal epithelial cells, being considered as one of the major entry route of SARS-CoV-2.

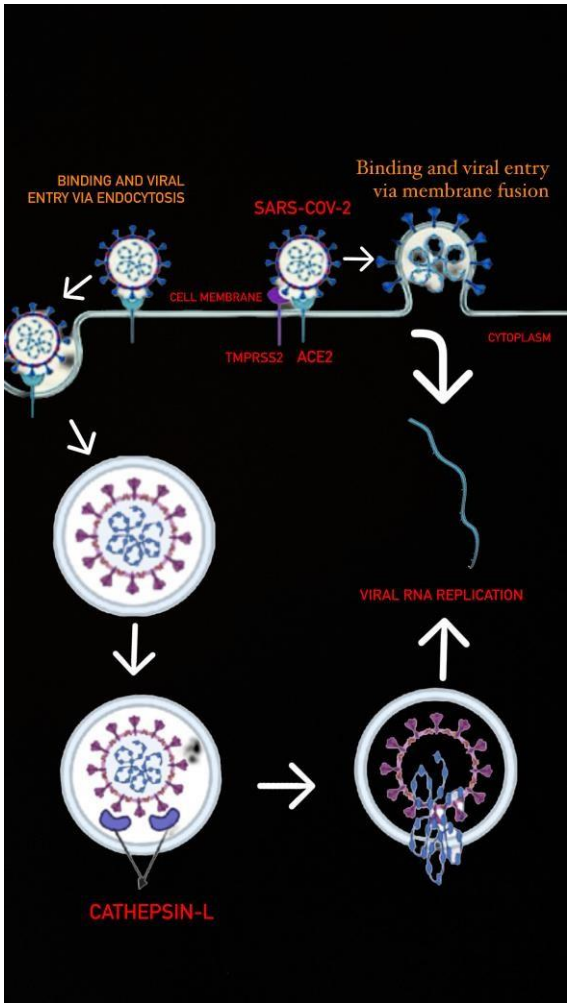
Immunostaining of cells harvested by liquid-based cytology from the gingival sulcus confirmed ACE2 expression in gingival cells collected from the gingival sulcus, which was stained at the same level as the tongue (which may be considered as one on the main SARS-CoV-2 entry routes along with salivary glands). The expression of SARS-CoV-2 entry factors is not a unique condition for the invasion, and these results should be analysed with caution. Recent studies have suggested that structural variations in human ACE2, producing spatial orientation changes of the key ACE2 interacting residues, may influence its binding with the SARS-CoV-2 spike protein. [23] [24]

Suryamohan K et al.,2021 explains that Functional role of the virus entry factors can be also reflected in block of SARS-CoV-2 invasion via ACE2 produced by TMPRSS2 inhibitor. [25] The expression of ACE2, TMPRSS2 in the sulcular epithelium and periodontal pocket epithelium along with the microenvironment of periodontal pockets as well as gingival sulcuses may also provide favourable conditions for virus replication and maintenance. [26]

Periodic changes during the SARS-associated Infection :

Some preliminary observation suggests that SARS-CoV-2 virus itself can modulate expression of ACE2 in

Figure -1:Penetration of SARS COVID -2 virus into the oral cavity



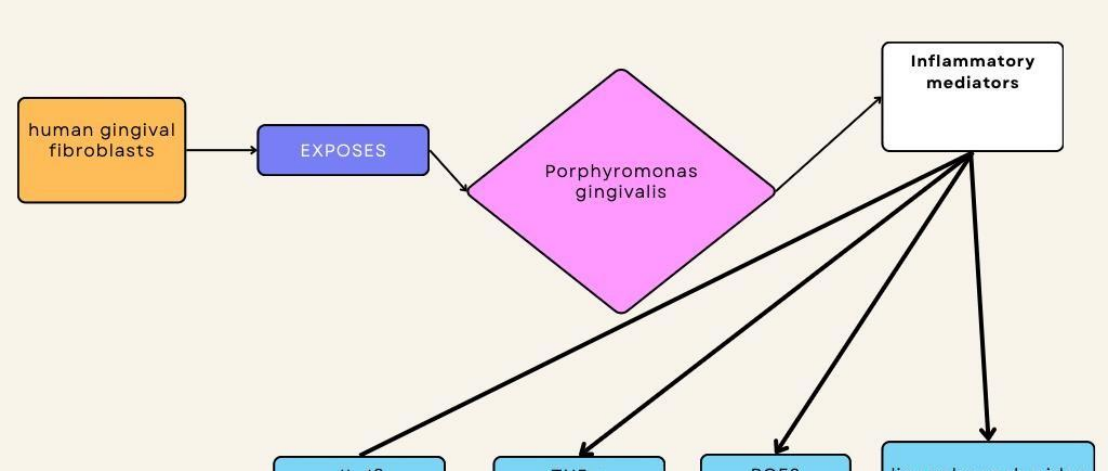
the oral mucosa (buccal) smear samples, and Covid-19 patients demonstrated downregulation

of ACE2 RNA, therefore, is can be hypothesized that the cellular response to SARS-CoV-2 may be of defensive nature, protecting a cell from the virus overload. (Smillie CS et al.,2019)[27].

The oral cavity tissues, including periodontium, can be the first to be infected with SARS-CoV-2 and oral lesions could be the first manifestations of Covid-19. So, dental practitioners could play an important role in the disease initial diagnosis, verified further by patients testing. [28] Invasion of the gingival epithelial cells principally via the ACE2/TMPRSS2 mechanism may affect the function of oral epithelial cells, finally resulting in ulcerated gingival lesions. A post-mortem study in patients diagnosed with severe Covid-19 evidenced histopathologic abnormalities and showed alterations in keratinocytes of the junctional epithelium, characterized mainly by vacuolization of the cytoplasm in the samples harvested from interproximal mesial papilla of first upper molar.[25] However, the observed

changes cannot be directly ascribed to SARS-CoV-2 infection, and/or severe systemic mechanisms could also be postulated to be involved, as the virus infection and replication is associated with inflammation and local immune cells activation. Badran Z et al.,2020 states that SARS-CoV-2 direct cytopathic effects were demonstrated in other epithelial cells, and this activity may also be operating in the periodontal tissues, contributing to local inflammation. [29]Inflamed gingival tissue of the Covid-19 patients contains elevated levels of proinflammatory cytokines, such as IL-1β and TNF-α.

Disturbed function of the immune system being a consequence of local and systemic SARS-CoV-2 infection may promote expansion of periodontal pathogens in periodontal pockets, for example, Prevotella intermedia, Streptococci, Fusobacterium, with a known consequence of acute periodontal conditions development. (Diamond G,2021 & Petrescu N,2022) [30][31]. Further events, like in a vicious circle, can include expansion of the SARS-CoV-2 entry and processing factors in human gingival fibroblasts induced by periodontal pathogens, that is, Porphyromonas gingivalis or inflammatory cytokines/mediators. Exposure of human gingival fibroblasts to Porphyromonas gingivalis-derived lipopolysaccharide (PgLPS) or IL-1β, TNF-α, PGE2 resulted in significant elevation of ACE2[31](Flow chart -1). Likewise, Doyle ME et al.,2021 has shown that the expression of TMPRSS2 was increased by some inflammatory mediators, that is, PgLPS, IL-1β or PGE2. The expression of FURIN decreased after TNF-α treatment. [32] These findings suggest that local inflammation in gingiva may promote local infection spread and viral replication in periodontal structures, with potential further systemic expansion. A periodontal intervention may decrease the expression of ACE2 and other SARS-CoV-2 entry and transmission factors in gingival tissues and gingival sulcus, thus prevent the virus attachment and internalization as well as local replication. [32]



Flowchart-1 .Petrescu N, Lucaciu O, Roman A [31]

Periodontal healthcare during COVID-19:

The periodontium infection by SARS-CoV-2 may initiate local inflammation, which can promote periodontal pathologies. Aspiration of oral secretions associated with periodontal disease (containing microorganisms such as P. gingivalis, F. nucleatum, P. intermedia) potentially can produce contamination of lower airways and infection. [30]

Likewise, cytokines (e.g. IL-1β and TNF-α) from periodontally diseased tissues can infiltrate saliva and be aspirated, and thus cause inflammation or infection within the lungs. (Botros N et al.,2020)[33]. Therefore, adequate oral hygiene could reduce the inter-bacterial exchanges between the lungs and the mouth, decreasing the risk of respiratory infections and potentially post-viral bacterial complications.[34] Reduction of oral inflammation can also contribute to better SARS-Cov-2 infection control affecting favourable microenvironment in periodontal pockets, and reduce cellular entry of the virus . Likewise, poor oral hygiene results in the formation of niches, which retain the virus being possible sites of favourable virus retention. A tight oral hygiene control may reduce viral particle load in the oral cavity/periodontium. In preliminary clinical observations Sena K et al.,2021 suggests that improvement of oral care can decrease the time of oral viral shedding[35]

There is also some evidence from clinical studies that application of oral antiseptics could support elimination of SARS-CoV-2 from the oral avity. [36]Povidone-iodine, hydrogen peroxide and cetylpyridinium chloride are the most recommended oral antiseptics against SARS-CoV-2. These agents were shown to decrease viral load in saliva for up-to 2–3 h post mouthwash in up to 50% of Covid-19 patients. Based on the evidence collected so far, it may advisable to use antiseptics, especially prior to the oral examination/treatment, that is, 0.2% povidone-iodine, 0.05%–0.07% cetylpyridinium chloride or 1% hydrogen peroxide.(Paju S, et al.,2007) [36] Likewise to antiseptics, general ingredients of toothpastes and mouthwashes might be able to affect the SARS-CoV-2 spike protein interaction with ACE2 and TMPRSS2 protease activity.In vitro assays detected inhibitory effects of sodium tetradecene sulphonate, sodium N-lauroyl-N-methyltaurate, sodium N-lauroylsarcosinate, sodium dodecyl sulphate and copper gluconate on the interaction between receptor-binding domain of spike protein and ACE2. Molecular docking simulations revealed that these agents could bind to inhibitor-binding sites of ACE2[37]. Sodium tetradecene sulphonate, sodium N-lauroyl-N-methyltaurate, sodium N-lauroylsarcosinate, sodium dodecyl sulphate, copper gluconate and tranexamic acid produced also inhibitory effects against the serine protease activity of TMPRSS2. Thus, oral hygiene with commonly available toothpastes and mouthwashes might be useful in prevention of SARS-CoV-2 infection and interfere with Covid-19 complications development and improve the disease course. [37,38](D'Aiuto F,2013

& Warabi Y,2020).

CONCLUSIONS:

Periodontal pathologies, especially periodontitis, could impact SARS-CoV-2 infection. Periodontitis can promote local infection and spread of the virus and vice versa local SARS-CoV-2 effects within the periodontium may favour development of periodontal pathologies. However, the latter phenomenon requires further studies. Implementation of periodontal health control and treatment might prevent the virus attachment, internalization and local replication in the periodontium as well as impact progression of Covid-19. Further efforts should be directed to verify and establish a local pharmacotherapeutic approach targeting SARS-CoV-2 in the oral cavity. Immunization of dental professionals is "strongly" encouraged by dental societies (e.g. American Dental Association), and was demonstrated to reduce the risk of SARS-CoV-2 infection in health care workers. However, it is not known how vaccination against SARS-CoV-2 affects periodontal status in health and disease. It can be assumed that vaccination triggers immune system responses, which more efficiently control the virus infection, reduces local inflammatory processes in gingival tissues and thus contribute to periodontal disease prevention.

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