Oral microbiome, COVID-19 Infection, and Oral hygiene

Subjects: Microbiology

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The oral microbiome plays an important role in the maintenance of immune homeostasis, whereas its association with SARS-CoV-2 infection remains under investigation. Since the oral path is one of the transmission routes for COVID-19, researchers attempt to show the relationship between the oral microbiome, COVID-19 infection, and oral hygiene.

COVID-19 Oral hygiene Oral microbiome

1. Introduction

Corona Virus Disease 2019 (COVID-19), or severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is caused by a novel coronavirus that started in Wuhan, China in December 2019 [1][2] and rapidly spread all over the world. Th World Health Organization (WHO) declared COVID-19 a global pandemic in March 2020, and it resulted a prolonged lockdown, economic crisis, and caused approximately 6,656,601 deaths globally by 12 December 2022 [2][3][4]. The common symptoms of the disease are fever, headache, dry cough, sore throat, and sneezing, which appear after COVID-19′s incubation period of 2–14 days (median, 4 days) and have changed with virus variants over time [3]. The intensive research literature of the last two years shows the cause, transmission route, virus variants, cell–virus interaction pathways, and their effects on the human body. Since SARS-CoV-2 is a pathogenic virus, the lungs are the primary organs that become exposed to the virus and are damaged if not treated urgently and properly. Several pathways of virus–human cell interaction have been highlighted in recent research; however, the mechanism of how the virus interacts with the microorganisms present in the lungs is still under investigation. Human lungs and airways harbor diverse microbial compositions which could be changed during severe respiratory infections such as COVID-19. Modern metagenomic and next-generation sequencing (mNGS) techniques helped in identifying lung-microbiome diversity in health and disease. Unlike the gut microbiome, the lungs microbiome is more dynamic and transient because of its bidirectional connection with the oral microbiome through the continuous movement of air and mucus exchange between two organs. A recent metatranscriptome sequencing to determine types of bacteria present in the bronchoalveolar lavage fluid (BALF) of eight COVID-19 patients revealed the presence of high levels of commensal bacteria in the oral and upper respiratory track compared to the control sample [5], indicating a significant relationship between the oral and upper respiratory track microbiomes in health and disease.

2. A Three-Dimensional Relationship between Oral Microbiomes, COVID-19 Infection, and Oral Hygiene

The oral microbiome resides in the oral cavity and co-evolves with the host tissues. This is controlled by a bidirectional interaction between the microbiome and the host. For instance, some bacterial species within the oral cavity, such as strains of *Streptococcus* (*S.*) mutans, can stop the invasion and the potential growth of harmful endogenous microbial agents by producing antimicrobial peptides known as bacteriocins [6]. Bacteria in the oral cavity are systematized in a structure called “biofilm”, which is a complex protecting structure in which bacterial groups exist in an extracellular matrix to protect themselves from external agents [6]. Therefore, oral bacteria provide the best environment to increase the rate of their growth within the oral cavity, as well as increasing the rate of pathogenic bacteria which lead to oral diseases. As a result, an immune system with intensive oral health care keeps the pathogenic bacteria under control and prevents problems such as tooth decay and gingivitis.

Saliva plays a critical role in preserving oral health and controlling healthy oral microbiota since it has organic and inorganic compounds. It provides an acquired hard glossy substance which covers the crown of a tooth, called enamel, and mucosal, which are the basis for the initial colonization by the microorganisms. In addition, saliva dilutes and removes microorganisms and dietary components from the mouth. It maintains the microbial environment via the antimicrobial action of particular proteins, such as peroxidase, and lysozyme [7]. That is why people (older adults) who have a low level of saliva production seem to have a high risk of getting dental caries [8].

Recent studies show a prevalence of oral bacterium within the oral cavity of healthy individuals such as Firmicutes, Proteobacteria, Bacteroidetes, and Spirochaetes [7][8][9], whereas they found less abundant fungal such as microbes of the genera Candida. The study investigates the variety in the composition of the bacterial oral community among ten healthy individuals [7][8][9]. It confirms that 15 bacterial classes were conserved between all individuals, with significant differences at the species and strain level. Moreover, sometimes, fungi, archaea, and viruses alter the environment of the oral cavity through their interactions with biofilms, which maintains health or changes the stability of the resident oral microbiome. For example, *Candida* (*C.*) *albicans*, the most common fungal colonizer in the mouth, interacts with oral bacteria. Various oral bacteria, such as *Staphylococcus aureus* and *S. mutans*, stick to *C. albicans* in oral biofilms and can control its pathogenicity. Furthermore, because the presence of *C. albicans* can affect how the bacterial microbiota behaves, these interactions are defined as being multidirectional [7][8][9]. As a result, the sum of all the microorganisms’ interactions may lead to the extreme complexity associated with these multispecies oral biofilms. It has been discovered that *C. albicans* interacts with *Porphyromonas (P.) gingivalis*, a significant etiological factor in chronic periodontitis [7]. This microbial complex influenced human immunity by reducing fibroblast and macrophage responses, whereas cytokine and chemokine significantly decreased compared to pure bacterial infection. The fibroblasts obtained from patients with severe periodontitis were less prone to fungus colonization, showing that the predominating bacterial infection modified the host environment [10]. Researchers draw the conclusion that a milder inflammation at the site of infection may result from the co-infection of *P. gingivalis* with *C. albicans.*

Viruses such as SARS-CoV-2 can directly or indirectly infect mouth tissues of either the mucosa or salivary glands. SARS-CoV-2 invades the host tissues by a helper entry receptor called angiotensin I-Converting Enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) [11][12]. Recent studies have documented the expression of *ACE2* found at a high level within several oral epithelial clusters such as salivary glands (SG) ducts, SG serous and SG mucous acini clusters. In addition, *TMPRSS2* was detected to be enriched in the SG epithelia. These results imply that a variety of oral-epithelial-cell subtypes are prone to infection, and they may transfer the coronavirus by their ciliary characteristic [12][13][14][15]. Therefore, since these two receptors are found at a high level in the oral tissue, they may serve as a vehicle for SARS-CoV-2. As a result, TMPRSS2 and ACE2 are traversing and establishing the route of SARS-CoV-2 transmission from the mouth to the respiratory system [12][13][14]. In addition, Huang and his colleagues reported that these two proteins, TMPRSS2 and ACE2, are detected within the lung in COVID-19 patients [15]. Moreover, some studies have used animal models, such as macaque, to study the SARS-CoV-2 infection mechanism [16][17]. They used a combination of intratracheal and intranasal methods to administer a SARS-CoV-2 strain to young and old cynomolgus macaques, resulting in an illness that resembled COVID-19 [16][17]. SARS-CoV-2 RNA was detected in numerous tissues from the tracheobronchial lymph nodes, ileum, and respiratory tract during the autopsies of four macaques. Acute or more severe diffuse alveolar damage (DAD)—which includes alveolar edema; epithelial necrosis; the formation of hyaline membranes; and an accumulation of neutrophils, macrophages, and lymphocytes—was present in two (old) out of four macaques, suggesting that age may play an important role in severe COVID-19 disease [16][17]. It seems that the nasal route is one of the transmission routes of SARS-CoV-2 in macaque. Another study has been carried out on ferrets, and ferrets were susceptible to SARS-CoV-2 infection and might spread the disease through direct or indirect contact (airborne transmission) with other ferrets. The lungs, trachea, gut, and kidney tissues of ferrets all had viral RNA. Importantly, the bronchial epithelium, bronchial lumen, and alveolar wall of infected ferrets showed increased immune infiltration and cellular debris, suggesting that SARS-CoV-2 infection could lead to acute bronchiolitis in ferrets [18]. Researchers suggest that the route of SARS-CoV-2 transmission in macaques and ferrets is similar to the human: starting from the nasal and oral cavity to the respiratory system.

Some cross-sectional studies have suggested that patients with COVID-19 show dysbiosis of the oral microbiome. Scientists noticed a decrease in the diversity of oral microbiomes is associated with the severity of COVID-19. In addition, the oral microbiome is correlated with a decreased level of IgA, which is the first line of defense against bacterial or viral infection, and increases the level of inflammatory cytokines [1][15][19]. Moreover, Bezstarosti et al. found that the severity of COVID-19 is correlated with upregulation of heparin cofactor II [20]. Researchers conclude that COVID-19 may manipulate the immune system of the host since heparin cofactor II plays an important role in immune response. It has been linked to leukocyte-mediated protein breakdown, which causes neutrophils and monocytes to produce cytokines during an inflammatory response [20].

One proteome study has been performed to identify specific interactions between proteins in SARS-CoV-2 and human proteomes. Gordon and his colleagues were able to detect 332 protein interactions between proteins in the SARS-CoV-2 and human proteomes using affinity purification mass spectrometry (AP-MS) [21]. Another proteome study reported that the differential regulation of 27 proteins identified by liquid chromatography with tandem mass spectrometry (LC-MS/MS) was also related to the severity of COVID-19 [22]. In addition, the cross-linking method

has been utilized to structurally investigate proteins within SARS-CoV-2, including: Nsp1, Nsp2, and nucleocapsid (N) proteins, to determine full-length atomic models. The full-length Nsp2 could be represented by a single reliable all-atom model according to the study, and its cross-links revealed a complex topology with long-range interactions. The replication–transcription complex has three putative metal-binding sites which are indicative of Nsp2's function in regulating zinc, according to the model. For the N protein, many intra- and interdomain cross-links were found [23]. Shen et al.'s study used Tandem Mass Tag pro, a chemical tag used for the detection of proteins in samples, combined with (LC-MS/MS), to determine which apolipoproteins in COVID-19-positive blood serum samples are regulated abnormally. Apolipoprotein A1 (APOA-I) and Apolipoprotein M (APOM) are significant in severe COVID-19 cases [24]. Therefore, these proteomic studies could help in the diagnosis and treatment of COVID-19. The cross-linking method offers important stereochemical and electrostatic data on proteins, as well as structural information to emphasize their significance in the cellular context. Researchers conclude that the identification of these case-severity-related proteins/protein-related entities could control the potential severity of COVID-19 cases before the disease develops into a severe case.

One study found an increase in the diversity of oral microbiomes in patients with periodontal diseases and dental caries. On the other hand, there is a decrease in the diversity of oral microbiomes in patients with smoking habits and oral cancer [13][25][26]. Therefore, oral pathogenic bacteria such as the status of periodontal disease and dental caries are affected by the diversity of oral microbiome. In addition, one study was performed in Nigeria on children with HIV. They found that HIV infection and treatment can affect the oral microbiome, which leads to an increase in the state of dental caries in a child [26]. However, the mechanism is not fully understood. In addition, the effect of SARS-CoV-2 on the diversity of the oral microbiome remains to be fully understood. Researchers suggest that SARS-CoV-2 may increase the level of pathogenic bacteria and decrease the level of useful bacteria with poor oral hygiene. As a result, it could cause weakness in the immune system in the body.

The oral cavity acts as a gate and exit for numerous respiratory infections, such as SARS-CoV-2 infection. Usually, SARS-CoV-2 is detected within saliva samples and an abundance of ACE2 receptors in the epithelial cavity [13]. The correlation between pathogenic oral microbiomes and the pathogenesis of respiratory infections has been investigated and several mechanisms have been presented. For example, *Porphyromonas* (*P.*) *gingivalis* is noticed at a high level in patients suffering from periodontitis; this results in lung infections by the aspiration of *P*. *gingivalis* into the lungs. Moreover, periodontal pathology results in modification of the oral mucous membranes made by inflammation [27][28]. In addition, periodontal diseases and chronic systematic diseases such as diabetes and hypertension have been identified as risk factors for severe SARS-CoV-2 infections. There may be a connection between COVID-19 and the complications of periodontitis since the cytokine storm brought on by the COVID-19 infection is very similar to the cytokine imbalance involved in the onset of periodontitis. Chemokines are responsible for the recruitment of inflammatory cells in both COVID-19 and periodontitis [29]. As a result, the pathogenic microbiome could be more subject to adhesion and colonization by pathogenic species of the respiratory tract, followed by their aspiration into the lungs.

Some studies reported that there is a relationship between SARS-CoV-2 infection, oral microbiomes, and oral hygiene. The role of TMPRSS2 is to break the S protein of the SARS-CoV-2 in order for it to fuse with the host cell

[27][28]. Besides TMPRSS2 in the oral cavity, the S protein of the SARS-CoV-2 can also be cleaved by pathogenic bacteria found in the oral cavity such as periodontal pathogens able to produce proteases to cleave the S protein of SARS-CoV-2 [2][25][26][30]. Periodontal pathogens are increased by poor oral hygiene, and these pathogens can enhance the expression of ACE2, boost pro-inflammatory cytokines, and degrade the S protein [27]. The penetration and infectivity of SARS-CoV-2 may be increased by the microbial proteases' destruction of the S protein [25]. COVID-19 can be made worse by neglecting dental hygiene and aspirating periodontal infections [27]. Therefore, pathogenic bacteria in the oral cavity can interfere with TMPRSS2 and ACE to facilitate the entry of SARS-CoV-2 into the host cell. Researchers can conclude that there is a direct relationship between SARS-CoV-2 infection, oral microbiome, and oral hygiene. In addition, maintaining good periodontal health may reduce the host's vulnerability to COVID-19 and help individuals with the infection avoid COVID-19 aggravation.

Zheng et al. found that in most severe COVID-19 patients, there was an increase in neutrophils and a decrease in lymphocytes, which is crucial in the immune response to viral species. This is an abnormal condition for viral infection. They expected the reason for the increased level of neutrophils to be due to bacterial co-infection and a decreased level of lymphocytes due to a dysfunction of the lymphocytes or the evasiveness of bacterial co-infection [31]. Another study confirmed that 50% of COVID-19 patients, who died, had a secondary bacterial infection [32]. In addition, one study showed the probable effect of oral bacteria in COVID-19 co-infections [33]. A recent metagenomic analysis confirmed a high level of cariogenic and periodontopathogenic bacteria such as *Fusobacterium* in COVID-19 patients [34]. These studies suggested that there is a correlation between the oral microbiome and SARS-CoV-2. It seems that poor oral hygiene may increase the risk factor for COVID-19 complications.

Improving the role of oral health and spreading awareness of oral hygiene could help in avoiding SARS-CoV-2 infections. Since most of the bacteria that cause complications in patients with COVID-19 are present in the mouth, adequate oral hygiene could be the best way to prevent and decrease the risk of acquiring a bacterial superinfection [35]. Oral health is very important, especially for ICU patients. One study found that ICU patients with COVID-19, who do not receive any oral care such as tooth brushing or rinsing of the mouth with water, accumulated hundreds of species of bacteria in their oral cavity. Therefore, they contracted both bacterial and viral infections which may lead to death if are not treated efficiently [1]. Researcher's suggestion here is for each patient in the ICU to be provided with a dental assistant to provide the best oral health care and avoid bacterial infection, especially for COVID-19 patients.

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