Influence of oral microbiome, gut microbiome and pulmonaire microbiome with COVID-19: review

Vitória Peixoto[1], Isadora Moraes[2], Orlando Santiago[3]
Arnaldo Dental School, Belo Horizonte, Brazil
[1]Corresponding author
E-mail: [1]*viitoriacarolaine@gmail.com*, [2]*isadorahelena2016@gmail.com*, [3]*osjofm@gmail.com*

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Abstract. The following document consists of a literature review that tries to relate oral, intestinal and pulmonary microbiome with complications of COVID-19, showing a significant part as a cause of death. The study tried to correlate viral respiratory infections with a second bacterial superinfection, which could be related to periodontitis.

Keywords: intestinal microbiome, pulmonary microbiome, oral microbiome, periodontitis, COVID-19, pneumonia.

1. Introduction

This bibliographic research is inserted in a group of reflections regarding COVID-19. It is known that SARS-COV-2 is a virus from the group of coronaviruses, classified as beta coronavirus SARS-COV-2 and being very similar to beta coronavirus SARS-COV and coronavirus MERS-COV. They differ by its capacity to adhere to the cells of the host. The virus SARS-COV-2 which causes COVID-19 appeared at the end of 2019 in Wuhan (China), with 27 cases of pneumonia related to a live animals wholesale market, with unknown causes [1].

Initially the disease showed a high contamination rate in men over 50 years old, as demonstrated by the Wuhan Hospital which evaluated 99 patients that showed symptoms such as fever, myalgia, mental confusion, headache, sore throat, rhinorrhea, chest pain, diarrhoea, nausea and vomiting (with predominance in male death) [2].

SARS-COV-2 is transcribed in a single RNA strand, which means it can have a bigger mutation compared to a virus with DNA. The SARS-COV-2's capacity to enter the cell is allowed mainly by the binding of the virus protein spike with the ACE2 receptor as a facilitator for the entrance in host cells. The ACE2 receptor can be found in the nasal mucosa, where the viral multiplication takes place and the immune system acts on the infection (in this moment the immune system should react in order to interrupt the infection). In case the infection is not stopped, the virus can migrate to the respiratory tract and lung alveoli which are filled with ACE2 receptors, and if this happens the leukocytes will migrate due to the action of cytokine action, resulting in the disruption of gas exchange [3].

Factors like age, gender and pathogenic comorbidity can increase the risk of COVID-19 complications, although this has been noticed the aggravation in patients conditions that were not considered to be in groups of risk. As a matter of fact, it is suspected that COVID-19 complications can be worsened due to bacterial infections [4]. The superinfection can be related to periodontitis [1] considered to be a bacterial disease and it can lead to a predisposition of various diseases which are considered risky diseases by the World Health Organisation (WHO) for example pneumonia and diabetes mellitus [5]. In addition, an intestinal dysbiosis can be caused resulting in the alteration of the immune response, having a negative effect in the process of stopping the viral infection [6] showing the systemic impact that periodontal disease can have in the organism.

According to the studies [7], the Porphyromonas gingivalis translation can make it easier for the replication of SARS-COV-2 across different mechanisms, acting as an entrance facilitator. Periodontitis was associated in 95 % of the cases in a research with 568 patients (including the

number of deaths), and it showed the direct relation between both diseases [1]. The hyper-inflammation caused by COVID-19 can create a convenient environment for the growth of oral pathogens, causing tissue damage in the oral cavity. Furthermore, there were many cases of patients post SARS-COV-2 that showed oral lesions, irreversible pulpitis and gingivitis [8], [9].

Patient control post COVID-19 is essential to maintain the person's health, especially the oral cavity. The relation between SARS-COV-2 and periodontitis is becoming more evident, since virus samples have been found in patient's saliva after those diseases. In addition to this, the influence is mutual as during COVID-19, a huge amount of cytokines can have an effect, causing the secretion of IL6, IL1, IL-β and TNF-α, taking place in an inflamed environment, which is typical of periodontitis that may have been caused by this virus [10].

Other oral lesions were reported in patients post COVID-19, as a highlight: lack of taste, xerostomia, ulcers, pain in the oral cavity, desquamative gingivitis and mucosal damage [8], [9].

This study has as main purpose to understand the relation between the microbiome and its role on COVID-19 complications. Among the specific purposes there are: to relate the intestinal microbiome with viral infection, to relate oral microbiome and lung microbiome, to understand how periodontitis can lead to intestinal, oral and lung microbiome dysbiosis.

2. Methodology

The literature review was accomplished by researchers in articles based on data from PubMed Scientific Electronic Library, Nature, Google Scholar virtual library. The research did not delimit a period of time between the articles. The languages used for the research were: English and Portuguese. The keywords used were: intestinal microbiome, pulmonary microbiome, oral microbiome, periodontitis, COVID-19, pneumonia.

3. Discussion

The virus is a particle composed of proteins and a type of nucleic acid (RNA or DNA), which can be cytopathic or non-cytopathic. Viral infections stimulate the production of interferon IFN through infected cells, which makes it an important viral inhibitor. Natural killer cells (NK) can lyse the viral cells, even when the virus inhibits the class I MHC expression [11]. Antibodies are also vital as they can be connected to the viral envelope, which can prevent its penetration in the cell and can act as opsonins, supporting phagocytosis. One of the main defence mechanisms against viral infections is lymphocyte mediated (Tc), which will lyse the infected cells and in certain occasions break viral particles [3]. SARS-COV-2, the virus that causes COVID-19 is a beta coronavirus with a simple non-cytopathic RNA which attacks mainly the respiratory system. This new coronavirus shows a very similar genome to SARS-COV, which happened in China in 2002 and also with MERS-COV [2] which happened in the Middle East in 2012. SARS-COV-19 attacks in different phases, which are:

I: the virus will attack the respiratory system, small intestine epithelium and vascular endothelium. All of those tissues are rich in ACE2 receptors (a receptor that can adhere properly to the virus, causing symptoms such as fever, dry cough and fatigue, as well as gastrointestinal symptoms). Those symptoms in phase I can be observed up to five days after being contaminated [3].

II (pulmonary): in this phase usually takes place a viral pneumonia condition. Hypoxia can take place or not, where patients can have a condition with the need for hospital internment, oxygen support and treatments [3].

III (hyper inflammation): this is when the disease changes into a pulmonary and extra extrapulmonary inflammation syndrome, where immune hyper-activation happens caused by inadequate elimination of macrophages activated and NK cells, as well as cytotoxic T lymphocytes, which leads to the excessive production of pro-inflammatory cytokines. This condition can lead to death if symptoms such as persistent fever, cytopenias, hyperferritinemia

and SRAG persists. By the time patients are taken to the ICU, they need to be intubated and placed on mechanical ventilation [3].

A hypothesis of a viral infection being able to initiate a second bacterial infection can be the reason for complications of COVID-191. This theory can be supported by the fact that 50 % of patients with severe COVID-19 died because of a secondary bacterial infection [2], [12].

Furthermore, other respiratory diseases such as the influenza pandemic in 1918, where the primary cause of deaths was not the virus itself, but a bacterial superinfection. The same happened in 2009 with H1N1, which again the main cause of deaths were a bacterial superinfection [1].

This research will link oral, intestinal and pulmonary microbiome, demonstrating how the dysbiosis of this group is related to the aggravation of COVID-19 conditions. In the periodontal condition can be observed a microbiome with predominance of bacterial colonies with high virulence which can reach other parts of the body through bacteremia, then influencing the other microbiome. In that way, this review will demonstrate how a weakened intestinal microbiome by periodontal disease can affect the organism response against COVID-19, worsening the disease.

3.1. Intestinal microbiome and the immune system

The effect of viral infection has been present in the intestinal microbiome [13], which leads to the possibility of the pulmonary and intestinal microbiome having an influence on each other, determining how the body will react towards a pathogen [14]. Nevertheless, when some of those microbiomes find themselves out of balance, the result is the dysbiosis of the digestive system and bacterial aspiration into the respiratory system, making it harder for the immune reaction. This intestinal dysbiosis (prior to a viral infection, as in COVID-19) can also be related to a superinfection, which is associated with chronic diseases, chronic characteristics of inflammation, abnormal metabolism, including cardiovascular problems, diabetes and even periodontitis [14], [15].

The relation between intestinal, pulmonary and oral microbiome can be the answer to COVID-19 complications as it is known that intestinal microbiome is responsible for the system's immune response, which means, a lack of equilibrium can affect the response of oral and pulmonary microbiome. [15] The intestinal microbiome is essential for the first immune response against viral infection, which is composed by actinobacteria and bacteroidetes, being responsible for the regulation of many physiological functions of the host, including dietary digestion and ensuring protective immunity against pathogens [15], [16].

Thus, the intestinal mucosa is exposed to a wide variety of antigens coming from food, resident bacteria and invading microorganisms, and those need to be limited by the mucosal barrier that provides immune defence to harmful antigens. The intestine commensal microorganisms induce the maintenance of important cells for the mucosal immunity. The immune system identifies the intestine commensal microorganisms and causes the immune response [14].

In some studies made by F. Sommer and F. Bäckhed, it was found that commensal microorganisms developed in germ free mice all over the immune system structure. The villi in germ free mice were distended and narrow, the depth of crypts smaller and less developed vascularisation. The intestine mucosa showed less B cells, T cells and dendritic cells, as well as premature mesenteric lymph nodes and immature and small Peyer's patches. During the colonisation with commensal microorganisms, it was observed in those animals a development of conformation linked to the immune system [17].

In addition, it is known that the bacterial colonisation in the upper respiratory tract is normally the first part of a bacterial infection [18] and also that periodontal microorganisms such as Prevotella - gram-negative bacteria, obligate anaerobes, Veillonella and Streck Opus 20 have the ability to colonise the upper respiratory tract [19]. That way, it is noted that an individual who has periodontitis has a disequilibrium between the intestinal and oral microbiome, which means the individual is more susceptible to the aggravation of other infections (such as viral infections) [20]. It was observed in a study with mice lacking microbiome an underdevelopment of

tissue-associated lymphocytes, a decreased number and size of Peyer's patches, mesenteric lymph nodes and defect in antibiotic production. This has led to an increased susceptibility of numerous infections including viruses, bacteria and fungi [19].

The dysbiosis or imbalance in the composition of the microbiome is associated with several chronic diseases, characteristics of chronic inflammation and abnormal metabolism, including cardiovascular disease, diabetes and periodontitis itself, since studies performed on patients with periodontitis the ingestion of high concentration of pathogens results in dysbiosis of the intestinal microbiome, favouring a microbiome with inflammatory profile [21].

In a study by Talita Gomes Beata Lourenço, the composition of oral and intestinal microbiome of patients with different periodontitis conditions were evaluated. The data demonstrated that the diversity of intestinal microbiomes is reduced in individuals with periodontitis. Furthermore, due to the sequencing of the 16S rRNA bacterial gene, there is a high prevalence and increased levels of oral pathogens in the intestinal microbiome in those patients [22].

Therefore, it is possible that periodontal pathogens could manage to resist the gastrointestinal system and reach the intestinal microbiome in order to cause a dysbiosis characterised by a reduction in the diversity of this microbiome [22]. A hypothesis is raised that patients with periodontitis in the group of risk causing COVID-19 complications (which could progress to pneumonia and even ARDS).

It is known that SARS-COV-2 has the ability to replicate throughout the whole organism. This is because, as well as affecting the respiratory tract, it can replicate in the enterocytes [23]. Thus, if the microbiome is in dysbiosis caused by other microorganisms (such as periodontal pathogens), the local immune response to a viral attack would be less efficient, which would also affect the entire immune's system response [24].

A meta-analysis of 60 studies, with a total of 4,243 patients showed that 17,6 % of the individuals who had COVID-19 showed gastrointestinal symptoms such as diarrhoea, nausea, vomiting, loss of appetite and abdominal pain. This would be the reaction of the intestine against a viral infection, the dysbiosis of the intestinal microbiome which is related to the reduction of diversity, due to inflammatory products and autoimmune diseases. [25] Periodontitis is related to this response, considering a study carried out by Bao J, who compared the presence of bacteria in the saliva of patients with periodontitis, which found that 52,38 % of these bacteria were found in the intestinal microbiome. This percentage was lower in healthy patients, showing evidence of the capacity of periodontal pathogens that lead to dysbiosis [6].

A dysbiosis of the intestinal microbiome can be harmful to the organism's immune response towards an infection, which means, in case this occurs there is a worsening of the response against COVID-19. Studies have shown an important role for the commensal microbiome in antiviral responses in the lung, modelling the immune response in homeostatic conditions and during a viral infection [26].

3.2. Relation of the viral infection with a secondary bacterial infection

Studies have shown that a viral infection can cause a secondary bacterial infection. This hypothesis can be raised due to the detection of a bacterial co-infection, as occurred in 30 % of H1N1 cases in 2009 [19] and also in the 1918 pandemic where most deaths were caused by a bacterial superinfection, and not the virus itself [1].

Co-infection is discussed by several authors, linking microbiome imbalance with the emergence of an opportunistic infection. This mechanism of viruses and bacteria are complex, since they present multi-factors such as the interaction of the virus, bacteria colonisation and the immune system [27]. An example of this is that after contracting influenza, the mucosa/epithelium is damaged by the virus, which increases the colonisation of bacteria in the respiratory tract, leading to the deregulation of immune responses, providing higher susceptibility to secondary bacterial infection [1]. A possibility of aggravating the condition of viral infection comes from the oral microbiome, as demonstrated, it mentions that this microbiome is the main source for the

formation of microbiome in the lungs and the development of lung disease such as pneumonia, chronic lung obstruction, fibrous cyst, asthma and even lung tumours might be associated with pathological bacteria present in the oral cavity [28].

With functions similar to the intestine microbiome or oral cavity, bacterial communities which colonise the lungs aim to preserve the tissue, immunity and homeostasis of the organ. Lower respiratory tract infection is initiated by the epithelium contamination in the lower airways by inhalation of microorganisms in droplets aerosols or by aspiration of secretion associated with oral diseases (P. Gingivalis, F. Nucleatum, P. Intermedia) [29]. Having periodontitis more frequently, cytokines (IL-1 AND TNF) from periodontitis can contaminate saliva through gingival crevicular fluid and if aspirated can cause lung inflammation [30]. 49,400 patients with chronic periodontitis were treated with periodontal therapy for 11 years, Kaplan-Meier demonstrated in a study that the incidence of pneumonia dropped drastically [29], [30].

Epithelial sensitivity and hematogenous dissemination of pro-inflammatory mediators such as cytokines (produced in periodontal disease tissue) can increase systemic inflammation and decrease airflow. This can be exacerbated by stimulating the liver to produce acute phase proteins, such as interleukin-6, which potentiate the inflammatory response in the lungs and the rest of the body [19]. Similarly, patients with severe COVID-19 infections also express systemic inflammation and significantly higher levels of interleukin-6, interleukin-2, interleukin-10, TNF and C-reactive protein. [20] In an ecological disorder or facing an oral disease, the microorganisms present in the oral cavity can migrate into the bloodstream or digestive system [31], [32].

This pathogenic microorganisms in the oral microbiome have the ability to enter the respiratory system with aid of the human body through: an accidental inhalation of oral saliva into the trachea, the act of sneezing taking the mucus from the respiratory tract into the mouth and also mutual exchange of substances in the oral cavity and respiratory tract. This would cause bacterial colonisation of oral bacteria, mainly Porphyromonas gingivalis, responsible for periodontitis. The result is a fragile system which when in contact with a more virulent pathogen could aggravate the situation [33].

In that way, it is observed that an individual with periodontitis has a high virulent capacity pathogen. When it is infected by SARS-COV-19, there is a favourable environment for its replication. The spread of periodontal bacteria to lung tissues can cause the induction of lipopolysaccharide senescence, which would facilitate SARS-COV-2 adhesion, therefore facilitating its replication. Altogether, pre-existing gram-negative bacterial infection and the associated presence of LPS can exacerbate local lung inflammation as result of SARS-COV-2 protein binding, increasing the activation of NF-KB [34].

4. Conclusions

The study shows the correlation of COVID-19 with the imbalance of pulmonary, oral and intestine microbiome. Periodontitis (a bacterial oral infection) has the potential to cause the disequilibrium to microbes not only locally, but in the organism generally.

Furthermore, it was observed the oral consequences that COVID-19 can trigger, aggravating the oral inflammatory conditions, making an individualised methodology essential in the treatment of patients who suffered from the disease. The microbiome has the ability to influence each other, and from the moment the individual contracts the SARS-COV-2 virus, it affects the immune system and microbiome will be in disequilibrium which facilitates bacterial infections by opportunistic microorganisms, including the worsening of periodontitis.

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Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

Vitoria Peixoto: conceptualization ideas, data curation, formal analysis, investigation, methodology, project administration, supervision, visualization, writing- original draft preparation, writing- review and editing preparation. Isadora Moraes: formal analysis, validation, visualization, writing- original draft preparation, writing- review and editing preparation. Orlando Santiago: Conceptualization ideas, data curation, methodology, supervision, writing- review and editing preparation.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics statement

The study did not involved the participation of human(s), biological material or their data.

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Vitória Peixoto undergraduate student of Dentistry from Faculdade Arnaldo Janssen, Belo Horizonte, Brazil, 2023. Her current research includes interest in relating COVID-19 to periodontics and occlusion.

Isadora Moraes undergraduate student of Dentistry from Faculdade Arnaldo Janssen, Belo Horizonte, Brazil, 2023. Her current research includes interest in relating COVID-19 to periodontics and occlusion.

Orlando Santiago Júnior is a Ph.D. student in Mechanical Engineering (Department of Mechanical Engineering) Universidade Federal de Minas Gerais Belo Horizonte, MG, Brazil. Now he works at dental office and is Associate professor at School of Dentistry at Faculdade Arnaldo Jansen, and School of Dentistry at Unicentro Promove, Belo Horizonte, MG, Brazil. His current research interest include jaw functional orthopaedics, temporomandibular disorders, dental occlusion and bite force measurement, bioengineering, nanomaterials