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COVID-19 AND PERIODONTAL DISEASE – ETHIOPATHOGENIC AND CLINICAL IMPLICATIONS

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Abstract

SARS-CoV-2 was first discovered in December 2019 as the etiologic agent of a serious respiratory illness later called COVID-19 or coronavirus disease 2019. The first COVID-19 case was reported in Wuhan, China and since then, has reached a pandemic level, spreading all over the world and multiplying faster than any other respiratory disease known until now in modern times, with more than 85 million confirmed cases and almost 2 million deaths, according to the latest information from the World Health Organization (WHO).

Periodontal disease is one of the most common diseases of the oral cavity that has systemic implications in the overall health homeostasis. It is an inflammatory disease that involves a series of dysbiotic events caused by periodontopathogenic microflora that causes destruction of the periodontal tissues locally, and an exacerbated proinflammatory status systemically. Diabetes mellitus, metabolic syndrome and obesity, hypertension, cardiovascular disease, chronic kidney disease, chronic obstructive pulmonary disease and autoimmune diseases have been identified as risk factors for both periodontitis and severe Covid-19 infections. These diseases have similar inflammatory pathways that are involved in the progression of these conditions, thus, it is fair to assume a pathological common link.

Keywords: *COVID-19, SARS-CoV-2, Periodontal disease, Cytokines, Immune system, Oral transmission*

1. Introduction

Covid-19 is a worldwide infection that challenged the functionality of every aspect of our lives, from healthcare to the economy to journalism to education. The velocity of the spread illustrated a challenge both for health care providers, policymakers and also higher education medical schools [1].

Coronaviruses belong to the Nidovirales order, which includes also Roniviridae, Arteriviridae, Mesoniviridae and Coronoviridae families. Coronaviruses have a specific complex RNA genome and causes a variety of systemic diseases in mammals going from respiratory infections, enteritis to fatal human respiratory illness [2].

Covid-19 it is a respiratory disease caused by a new type of coronavirus called SARS-CoV-2. The name coronavirus comes from the latin word "corona" and reflects the image of the virus seen under an electron microscope as round areas that

resemble with the solar corona. These viruses, pertaining to the coronavirus family were discovered in humans in 1965. Coronavirus belongs to the family Coronaviridae which, in general, gives the human host mild respiratory diseases. Lately, the human population encountered three major coronaviruses that caused major disease outbreaks, first is SARS-CoV appeared in 2002, followed by the Middle East respiratory syndrome coronavirus (MERS -CoV) in 2012 and the third and the latest: severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [3].

In December 2019, several cases of pneumonia of unknown etiology were reported in Wuhan, China. The outbreak began in early December and the number of cases increased rapidly. More than 80,000 cases were reported in China by March 15, 2020, with more than 3,000 deaths[4]. COVID 19 soon turned into a pandemic. Initial reports showed that although the majority of COVID-19 cases have a mild to moderate pathological response, approximately 20% of cases are severe and the fatality rate seems to depend on age and sex (higher percentage in the elderly and in men) [5].

Oral diseases such as carries and periodontal disease, are some of the most prevalent diseases globally thus they represent an important public health issue and exert major health and economic burdens for the socio-ecomomic interface, communities and also for individuals [6].

Periodontal diseases are a group of pathologies of an inflammatory nature in which a host response is induced by microbial etiologic factors that mediate inflammatory events, which lead to tissue destruction in susceptible subjects [7]. The global prevalence of severe periodontitis in 2017 reached almost 800 million people [8].

Periodontitis is an inflammatory infectious disease of a chronic nature that is multifactorial and it affects not only the supporting tissues of the dental unit but it also has nefarious systemic effects [9]. Escalading evidence in the literature indicates that periodontal disease is correlated to several chronic systemic diseases, due to the fact that it is a chronic low-burden inflammation. These pathologies include diabetes mellitus, metabolic syndrome and obesity, cardiovascular diseases, hypertension, chronic obstructive pulmonary disease, autoimmune diseases, Alzheimer disease and cancer [10-13]. All of these systemic diseases, with the addition of old age and smoking, have been described as risk factors for severe COVID-19 infections [14].

The purpose of this article is to draw attention to common pathological and inflammatory pathways between periodontal disease and COVID-19, and further imply that periodontitis could be a contributing or exacerbating factor for COVID-19 severity.

2. Epidemiology of COVID-19 and periodontal disease

The causative agent of the outbreak has been identified as a beta-coronavirus with a genomic sequence related to the 2003 severe acute respiratory syndrome coronavirus (SARS), called SARS-CoV-2. It is most likely derived from bats, but may be amplified by an intermediate host [3].

In the beginning of the COVID-19 pandemic, the transmission dynamics was considered to be via the exposure of the population to the wet markets [4], however, later in march 2020 the number of people who developed the disease without exposure to the wet markets has increased, and it was suggested that rather a man to man spreading of the COVID-19 was more plausible [15].

Similar to other respiratory viruses, the direct or indirect droplet borne infection is considered to be the principal way of spreading. The velocity of the spread of SARS-CoV-2 has been swift.

Already over 85 million people have been infected and almost 2 million people have died as a result of the disease globally [16]. Older individuals and those with comorbidities have a higher risk of developing a severe form of COVID-19 infection [17].

Another world resource consuming disease is represented by periodontal disease, which is the most commonly diagnosed oral disease. Periodontal disease has two stages, gingivitis and periodontitis. The first stage is reversible with the aid of dental prophylaxis, while the second stage, the irreversible one, represents an inflammatory disease of the deeper supporting structures of the tooth [9].

Periodontal disease develops when oral periodontopathogenic bacteria adhere to the teeth in the gingival socket and cause an immune response from the host. Bacteria are present as a planktonic form or in the bacterial plaque or biofilm, which is composed of salivary glycoproteins and extracellular polysaccharides [18].

Periodontal disease represents one of the most common diseases worldwide affecting 20% to 50% of the world population, according to certain studies [6, 19, 20]. If we take a look at the prevalence of periodontal disease we observe that it increases directly with age, and men have a higher prevalence and severity when compared to women [19].

The most important risk factors for periodontitis are represented by age, gender, hereditary factors, diabetes mellitus and smoking. Periodontal disease has been linked to certain systemic conditions such as pregnancy, menopause but also many systemic diseases like atherosclerosis, diabetes mellitus, and autoimmune disorders (such as AIDS or rheumatic diseases) via an increased level of serum C - reactive protein (CRP), a marker used in determining the level of inflammation in the body [21]. These same factors, with the addition of smoking as a major risk factor, have been also associated with COVID-19, and since the levels of CRP shows us the systemic proinflammatory status, it is possible that periodontal status may indicate the risk and the severity of COVID-19.

3. Ethiopathogenic mechanisms and diagnosis of Covid-19

Coronaviruses are a group of related RNA viruses that have a specific and complex genome and cause a variety of systemic diseases in mammals that can range from respiratory infections to enteritis to fatal human respiratory illness. The structure of a coronavirus is represented by membrane, envelope, nucleocapsid and spike proteins, these last proteins are important because when they interact with a specific cell receptor from the host and mediate the membrane passing process, the Covid-19 disease commences [22]. It has been reported in the literature that SARS-CoV-2 interacts with angiotensin converting enzyme 2 (ACE2) and dipeptidyl peptidase 4 (DPP4) [23]. This receptor is highly expressed in nasal goblet cells, ciliated airway cells, type II alveolar pneumocytes, enterocytes, renal tissues and cardiovascular tissues [24-26].

Some authors have reported in the scientific literature that the most frequent locations for the inoculation are in the upper aerodigestive tract, with the highest expression patterns of ACE2 being the oral mucosa, vocal cords, salivary glands and the sinuses, while lower levels of ACE2 were reported in the tonsils, pharyngeal and laryngeal epithelium [27].

Patients infected with SARS-CoV-2 can develop a wide range of symptoms such as fever, dry cough, shortness of breath, gastrointestinal and other symptoms, such as abdominal pain, diarrhea, anorexia, vomiting, myalgias, headaches, dizziness, anosmia, dysgeusia, sore throat, fatigue, and chills. However, the main clinical symptom remains pulmonary inflammation, and in more

severe cases tachypnea, dyspnea and also severe pneumonia can be present, which can trigger respiratory failure, septic shock and multiorgan failure [28].

The immune response in Covid-19 has two phases. The first phase is the body's' response directly to the viral infection, and the second phase is represented by the cytokine storm reaction and this causes autoimmune induced damage to lungs, gastric mucosa, brain and other structures. Infection with SARS-CoV-2 determines a complex activation of neutrophils, T helper 17 (Th17) cells, Th1 cells, dendritic cells and higher levels of Immunoglobulin-1 (IL-1), IL-6, and IL-10, IL-1β, IL-4, IL-10, Interferon- γ (INF-γ), Tumor Necrosis Factor–α (TNF-α), interferon gamma-induced protein 10, and monocyte chemoattractant protein 1 and these information led to the idea that high levels of ACE2 expression after infection were involved with immune system dysregulation and followed the cytokine storm [29]. A weakened innate immune system leads to a higher SARS-CoV-2 viral count, overresponse of the adaptive immune system and cytokine storm. In another study, the authors verified the connection between C-reactive protein and vitamin D and they found out vitamin D deficiency can exacerbate the response to the cytokine storm [30].

Other manifestations associated with Covid-19 are high levels of iron, lyphocytopenia, decreased platelet count, and high ESR (erythrocyte sedimentation rate) [31].

High reactivity of platelets and thrombotic reaction contributes to morbidity through increased platelet-leukocyte interactions. Children with COVID-19 present milder symptoms when compared to adults. More often observed symptoms include acute chest infections, pyrexia, dry cough, sore throat, sneezing, myalgia and lethargy. Another important syndrome associated with SARS-CoV-2 observed in children is multisystem inflammatory syndrome [32].

The positive diagnosis of COVID-19 is based on a molecular or antigen test that detects viral RNA and on a suggestive clinical history, including exposure history and clinical manifestations of SARS-CoV-2 [33]. Covid-19 initial stages clinically mimics any other viral respiratory disease, so infection with SARS-CoV-2 must be differentiated from influenza, parainfluenza, coronavirus, adenovirus, HIV and bacterial pneumonias. Pulmonary inflammation is the major pathologic manifestation of COVID-19 and patients should undergo a chest X-ray or CT scan examination in order to see if there are modifications such as peribronchial thickening or pneumonia [34]. However, CT should be reserved only to hospitalized patients with specific clinical indications for this evaluation [35].

Abnormal blood test results show higher levels of C-reactive protein, lactate dehydrogenase, ferritin, procalcitonin, creatine kinase, alanine aminotransferase, aspartate aminotransferase and low albumin [36].

4. Interactions between Covid-19 and Periodontal disease

Periodontitis represents an inflammatory disease that is associated with several chronic systemic diseases like diabetes, metabolic syndrome, asthma, cardiovascular diseases, hypertension, cancer, renal disease, autoimmune diseases, Alzheimer disease, Viral Hepatitis. All of these systemic conditions, plus smoking, have been described as being risk factors for severe infections with SARS-CoV-2 [5,7, 37].

Another important factor that could underline the connection between COVID-19 and periodontitis is age. Periodontal disease affects elderly people, because they have some associated risk factors such as: poor oral hygiene, longtime medication, chronic diseases, and from the

COVID-19 point of view, patients over 65 years represent a higher risk group due to chronic comorbidities and the weakened immune response [7, 38].

Hypertension is the main risk factor for cardiovascular disease and epidemiological studies demonstrated an association between hypertension, cardiovascular disease and periodontitis [39]. High density CRP is a marker present in cardiovascular diseases and also in periodontitis where is increased by large production of cytokines. Hypertension represents one of the main comorbidities to the COVID-19 patients [40].

Oral dysbiosis represents the loss of the balance of the oral microbial communities and it is associated with many oral diseases like periodontitis, candidiasis and others. The main bacteria involved in the appearance of periodontitis are *Porphyromonas gingivalis, Tanerella forsythia, Treponema denticola, Prevotella intermedia, Selenomona, Aggregatibacter* and others [41].

The series of events that develop in the oral cavity that lead to oral dysbiosis is a process called polymicrobial synergy, where bacteria interacts and causes tissue damage and complex inflammation [42]. Patients diagnosed with Covid-19 had higher levels of ACE2 on the oral mucosa and also an increased presence of *Prevotella, Fusobacterium, Veillonella*, therefore this could constitute an important proof of the link between periodontitis and Covid-19 [43].

Rheumatoid arthritis is a chronic inflammatory disease that has been correlated with periodontal disease, several studies showed that people with rheumatoid arthritis have a worsened systemic status if they suffer also from periodontitis [44]. With regards to the Covid-19 infection, the main concern of rheumatologists is the susceptibility of rheumatoid arthritis subjects of developing more severe symptoms. On the other hand the treatment with hydroxychloroquine for rheumatoid arthritis has also been reported as an effective treatment for certain cases of Covid-19, however further studies are necessary to assess its effectiveness for these patients [45].

The ethiopathogeny of cancer is not yet fully understood, however, according to some studies, it can appear due to microorganisms that increase the inflammation in the body. That being said, there is not enough evidence in the literature that establishes a causal link between cancer and periodontal disease [46]. There is however an increased susceptibility of cancer patients to develop Covid-19 infection due to their suppressed immune response, but also a more adverse outcome due to many other systemic issues like respiratory infections, nutritional problems and also vitamin and mineral absorption deficiencies [47].

Smoking is the most important risk factor in periodontal disease and it affects the disease progression but more importantly, it's response to periodontal treatment [48]. The key mechanisms that would give us the upper hand in the fight with periodontal disease and Covid-19 are crippled by smoking. Those mechanisms are the immune response of the host, the normal activity of periodontal tissues and a powerful microenvironment to fight against pathogens. Furthermore, smoking increases the expression of ACE2 and is an additional risk factor in the progression of Covid-19, but more studies are necessary to determine the real risk of Covid-19 among smokers [49].

Regarding the possible direct link between Covid-19 and periodontitis many studies have shown a potential connection, starting with the bacteria involved in COVID-19 infection that seems to be the same to those from the oral cavity. Periodontal affected tissues represent a wide entry point for bacterial or viral pathogens like SARS-CoV-2, due to the clinical manifestation represented by extended ulcerated areas. Also

periodontitis increases the systemic inflammation burden and this leads to the release of proinflammatory cytokines and tissue destruction mediators in the circulatory system [50].

The cytokine storm caused by the COVID-19 infection is very similar to the cytokine imbalance involved in the development of periodontitis, suggesting a possible link between COVID-19 and periodontitis complications [51]. In both Covid-19 and periodontitis the recruitment of cells of inflammation is caused by chemokines. In patients with Covid-19 hospitalized in the intensive care unit, elevated serum levels of IL-1β, IL-7, IL-10, IL-17, IL-2, IL-9, Th17, IFN-gamma, GM-CSF, G-CSF, IL-8, TNF-α, MIP1B, MCP1, MIP1A and IP10 were observed [29].

5. Dental practitioner recommendations

The best way of treating someone is prevention. Is highly important to respect social distancing and isolation in order not to transmit the infection. The more effective actions in order to reduce the risk of infection is washing hands frequently, home quarantine if you are infected, travel restrictions, use of masks to cover both mouth and nose when talking, sneezing or coughing.

Medical staff should prevent and control the infections during the SARS-CoV-2 pandemic, and the ways of preventing an infection should be explained carefully to every patient. Patients should be highly advised not to come to the medical, dental or any type of practice if they have symptoms of Covid-19 infection. Another important aspect is using triage protocols so that the medical staff can determine if the patient genuinely needs a physical doctor's appointment, or he can be investigated using telehealth strategies.

Considering the fact that some periodontal procedures are considered high risk, such as the use of water-air spray, sonic and ultrasonic scaling, polishing with rotary instruments and other aerosol generating maneuvers, practitioners are advised to limit as much as possible these procedures during these times and even postpone them if the patient is suspect of infection with SARS-CoV-2. Doctors and assistants must investigate every patient thoroughly for signs of Covid-19 infection, and these investigative actions must be made outside the clinic, in a separate building [51].

Medical staff should offer patients and workers, alcohol based 60-95% hand sanitizers and also tissues for personal use.

Patients with Covid-19 symptoms should be evaluated separately and they should not wait among other patients until he is investigated.

Others methods used for preventing infection with SARS-CoV-2 are represented by the oral mouthwashes, because they have the capacity of reducing microorganism load inside the oral cavity [52]. There are many mouthwashes that can be used, but the most effective are those with chlorhexidine 0.020%, due to the fact that it is effective on Gram positive and Gram negative bacteria and also on viruses like influenza A, parainfluenza, herpes virus 1, cytomegalovirus and hepatitis B. Other mouthwashes that can be used are those based on hydrogen peroxide, cetylpyridinium chloride and iodopovidone [51].

Conclusions. It is unclear until now if infection with Covid-19 offers immunity or for how long it lasts. Another issue is the fact that the presence of antibodies may not offer immunity. All in all, the best way of keeping healthy is by respecting the preventive measures.

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