Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Is periodontal disease a risk factor for severe COVID-19 illness?

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ABSTRACT

Periodontal disease (PD) comprises a group of diseases involving inflammatory aspects of the host and dysbiotic events that affect periodontal tissues and could have systemic implications. Diverse factors and comorbidities have been closely associated with PD such as diabetes, obesity, aging, hypertension, and so on; although, underlying mechanisms or causal associations have not been established completely. Interestingly, these same factors have been widely associated with progression or severe coronavirus disease 2019 (COVID-19), an illness caused by coronavirus SARS-CoV-2. Since inflammatory and dysbiotic factors as well as comorbidities affect systemic health, it is possible that periodontal status indicates the risk of complication of COVID-19. However, assessment of oral health history including periodontal status in COVID-19 patients has not been reported. Knowing PD is associated with severe COVID-19 could help identify risk groups and establish pertinent recommendations.

Introduction

Periodontal diseases are a group of chronic inflammatory diseases, including gingivitis and periodontitis [1–3]. These diseases are driven by several microbial agents that cause inflammation and destruction of tooth-supporting tissues [4]. According to the World Health Organization (WHO), PD affects 10% of the global population [5]. Poor oral hygiene, tobacco smoking, diabetes, medication, age, hereditary, and obesity have been related to increasing the risk of PD [6–8]. Similarly, other studies suggest the association between PD and other diseases such as diabetes, hypertension, asthma, liver diseases, among others [9–11].

COVID-19 is a disease caused by novel coronavirus named SARS-CoV-2 that triggers damage to the lungs and other organs [12]. Most COVID-19 patients present mild symptoms; however, a few could develop severe illness having pneumonia, pulmonary edema, acute respiratory distress syndrome (ARDS), multiple organ dysfunction syndrome, or even die [13]. There are other diseases like severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) by other coronaviruses that cause respiratory problems [12,14]. COVID-19 was declared a pandemic by the WHO on March 11th. At present, in May 2020, there are more than 3,000,000 infected people around the world. Of all infected, only a small percentage induces critical state, considering the presence of any comorbidity or condition, which can be diabetes, hypertension, obesity, asthma, pregnancy, lung diseases, liver diseases, oral dysbiosis, aging, and gender [12,15,16].

This work proposes to evaluate if PD could be a risk factor for developing severe COVID-19 illness because of shared risk factors.

Hypothesis

PD could be associated with severe COVID-19 illness. Oral medical history of PD could be a characteristic to identify a risk group to severe COVID-19. The suggested relationship between PD and severe COVID-19 illness could be connected to closely shared risk factors among these affections. Most comorbidities and risk factors reported in patients with severe COVID-19, also aggravate the development of PD. Until now, information on oral health history including periodontal status in patients with severe COVID-19 illness has not been reported.

Evaluation of hypothesis: Shared risk factors by PD and severe COVID-19 illness

Aging

Aging is considered a process that causes degenerative changes at the cellular level and sometimes leads to various diseases that can be

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autoimmune, infectious, or inflammatory, including PD [17,18]. According to the WHO, PD affects elderly adults, who are among the main target groups, because it is common that they have the following additional risk factors: poor oral hygiene habits, presence of chronic diseases, use of medications, smoking or lack of timely dental treatment, which can alter gingival microbiota and allow the development of PD and even respiratory infections [19–21].

People over 65 years are the highest risk group by severe COVID-19 illness, mainly for the multimorbidity which is a common factor in this group that allows the rapid attack of the virus and increase mortality [22]. Another critical factor for the disease to be severe is the immune response, which is not as strong compared to young people [18].

Therefore, it is clear that aging is a determining risk factor in linking PD and severe COVID-19 since they share the associated risk factors that can lead to complications, thus allows to identify risk groups to severe COVID-19.

Gender

Different studies have suggested that men are more prone to severe forms of PD than women [23–26]. It was proposed that differences in immune function could be involved; moreover, probably behavioral and environmental factors could have an important role to explain differences in gender, however this has not been well determined [26].

In a similar way, it was suggested that men are more prone to become seriously ill by COVID-19 than women [27–29]. Recently, it was proposed that differences of immune response to SARS-CoV-2 between men and women could explain this variance [28]. Thus, PD could show the risk of COVID-19 illness, considering its association with gender and possible immunologic factors.

Diabetes mellitus

Diabetes mellitus (DM) is a chronic disease determined by loss of control of glucose homeostasis that can affect the organs of the body (WHO). This disease is associated in a bilateral way with PD. That is, the PD can be a complication of diabetes by out of control the level of glycemia, and having diabetes increases the possibility of developing PD [30–32]. The proposed mechanisms to understanding this association include alterations in vascular, cellular, and host repair processes [33].

Increasing evidence supports an association between severe COVID-19 and DM, this is supported by chest tomography and other clinical parameters that state alterations in patients with diabetes [34,35]. Several studies show patients with severe COVID-19 may have affected expression of the angiotensin-converting enzyme 2 (ACE-2) in the lungs. This receptor is greater in diabetic than in no diabetic patients due to treatment with ACE inhibitors and angiotensin II type I receptor blockers (ARBs) [36,37]. In both periodontal disease and COVID-19 the response immune is affected by host factors, external and internal [37,38].

Diabetes is a significant predictor of severe COVID-19 and periodontal disease, so that the latter could be useful to identify risk groups of COVID-19.

Hypertension and cardiovascular disease

Hypertension is a health disorder that affects a large part of the population worldwide. High blood pressure (BP) is considered the main risk factor for cardiovascular disease (CVD) [39]. Epidemiological studies have shown an association between hypertension, CVD and PD [40]. The latter is currently considered a risk factor in hypertension and CVD [41–43].

In PD, the accumulation of various bacterial species in the subgingival biofilm induces a chronic inflammatory response by inducing the production of cytokines (IL-1, IL-6, IL-8 and TNF-a) [44], which regulate and increase levels of C-reactive protein (CRP). Detection of high-density CRP has been considered a marker in CVD and hypertension. In PD, presence of CRP is the link between these diseases [41,45,46].

Hypertension is among the main comorbidities in COVID-19 infection [47]. Treatment of hypertension with ARBs increases expression of ACE-2 [48]. Another study in EP showed that the activity of ACE and ACE-2 was increased in this disease [49]. Hao Xu analyzed seqRNA profile data and demonstrated that ACE-2 could be expressed in oral mucosal epithelial cells [50]. Therefore, the expression of ACE-2 in hypertension and periodontitis may represent a major risk factor for severe COVID-19.

Obesity

In industrialized countries, about 50% of the population is overweight or obese, with prevalence increasing annually. After smoking, obesity is the highest risk factor to develop PD, and its relationship has been studied since 1977 by Perslein and Bissada studying obese rats [51,52]. Different mechanisms linking PD and obesity have been suggested. Obesity can alter the periodontal microbial composition and is associated with an increase in periodontal pathogens [53]. The main consequence of obesity is a systemic inflammation state [51]. Adipose tissue typically secretes low levels of proinflammatory cytokines (IL-6, IL-8, TNF-α), adipokines like leptin and adiponectin [54]. These cytokines may contribute to the development of PD altering the response to bacteria in gingival tissue [53]. Additionally, the production of reactive oxygen species that generate oxidative stress is increased in obesity [55]; this is important, since oxidative stress is increased in PD and it could contribute to its progression [56]. If PD is established in individuals with obesity, there is an induction of an increased inflammatory systemic state triggered by the dissemination of bacterial products and proinflammatory cytokines [53].

Obesity and their complications increase the risk to develop severe COVID-19 illness [57–59]. Factors implicated in this association could be decreased expiratory reserve volume, functional capacity, and respiratory system compliance. Additionally, augmented inflammatory factors reported in obesity could contribute to amplify the response of the patient and develop severe COVID-19 [58,59].

PD could contribute to the amplification of a systemic inflammatory response by dissemination of bacterial products and as a source of inflammatory cytokines in patients with COVID-19, therefore aggravating the disease. Moreover, it is possible that individuals with obesity and PD have an increased risk of developing severe COVID-19.

Pregnancy

Pregnancy allows various physiological changes, [60] and suppresses the mother's immune system to allow gestational development. Over the last few years, some epidemiological studies have suggested the vulnerability of pregnant women to PD due to an affected inflammatory response [61,62]. Furthermore, it has been established that increased progesterone levels trigger the gingival response causing dysbiosis. In this way, high periodontopathogens growth occurs, [63,64] causing clinical manifestations in the supporting and protective tissues of the teeth. Although, the link between PD and pregnancy is controversial, some risk has been suggested among pregnant women and PD as they may have complications during pregnancy, [65] or premature delivery.

As long as the novel coronavirus SARS-CoV-2 is spreading worldwide, some cases of COVID-19 have confirmed in pregnant women. Although, immunosuppression, high progesterone and estrogen levels, and the physiological adaptive changes predispose pregnant women to respiratory infections diseases, [66,67] less than 10% developed severe COVID-19 disease [68–70]. However, this infection could complicate perinatal events such as preeclampsia, premature rupture of the

membrane, low birth weight even death [67,71]. Vertical transmission cases of COVID-19 are not fully confirmed [66, 67)].

Despite the fact, that the association between pregnancy and PD is not clear. Coinfection of SARS-CoV-2 in pregnant women with PD and other comorbidities could complicate pregnancies.

Chronic obstructive pulmonary disease (COPD)

COPD is a chronic inflammatory lung disease caused by important exposure to noxious particles or gases, being smoking a main risk factor in developed countries [72]. Different studies have associated COPD and PD [73–75], however, this link could be confounding by different factors like age or smoking. Recently, it was suggested that the severity of PD increases the risk for COPD mortality in older patients [75]; though, causality or involved molecular mechanisms have not been reported.

It was suggested that patients with COVID-19 have an increased risk of aggravation when they present COPD [76] and patients with pre-existing COPD have a 4-fold increased risk to develop severe COVID-19 illness [77]. It was proposed that the increased risk could partly be because COPD patients present increased expression of ACE-2 in airways [78]. Thus, the association of PD with COPD could be helpful to identify risk groups to develop severe COVID-19, since COPD increased importantly the risk of this affection.

Smoking

Smoking is a major risk factor to develop PD, and it affects the progression, severity and response to treatments of this condition. Different molecular mechanisms have been suggested to explain the contribution of smoking to progression of PD; smoking promotes dysbiosis in periodontal tissue, improving the virulence factors of key periodontal pathogens, favors the microenvironment to these pathogens and impairs the immune response of the host [79].

On the other hand, smoking is a risk factor of COVID-19 progression, being 1.4 times more probable to have severe COVID-19 symptoms [80]. Additionally, as COPD, smoking could increase the expression of ACE-2 [78]. It was proposed that smoking cessation could decrease the risk of developing severe COVID 19 complications [81]. However, relationship between smoking and severity of COVID-19 illness is not completely clear, since a *meta*-analysis suggested not association of active smoking to severity of COVID-19 [82]. It is possible that discrepancies could be due to absence of information (as smoking duration or current and ex-smokers) in all the analyzed reports [77]. Thus, more deep studies are necessary to determinate the real risk of smokers and progression of COVID-19.

Since it is well established that smoking history is association to PD and it could be associated to severe COVID-19 [77], probably, PD in smokers and comorbidities like COPD could identify a risk group to severe COVID-19.

Asthma

Asthma is characterized by chronic inflammation of airways and diverse studies have positively associated asthma and PD [83–86]. It was suggested that asthma could be a risk indicator for PD in adults. Even though, it not has been established causal relation or a molecular mechanism to explain this association, it was proposed that inflammatory factors and genetics [86] or dysbiosis could be involved. Moreover, it is possible that this association is related to a comorbidity or result of medication used for treatment [84].

It was proposed that asthma could be a risk factor for severe COVID-19 illness [87]; however, asthma had lower prevalence than that expected in COVID 19 patients [88]. Moreover, decreased expression of ACE-2, the cellular entry receptor used by SARS-CoV-2, was reported in patients with asthma [89]. It was speculated that lower prevalence might be due to underdiagnosis or lack of recognition of asthma in patients with COVID-19 [87,88]. Furthermore, asthma patients with DM presented increased expression of ACE-2 and TMPRSS2 (Transmembrane protease, serine 2), and in addition to ACE-2 receptor used by SARS-CoV-2, the entry to cells is dependent on the priming of the spike (S) protein of this virus by proteases of host as TMPRSS2. Thus, increased expression of ACE-2 and TMPRSS2 in these patients could indicate increased susceptibility for SARS-CoV-2 infection and COVID-19 morbidity [90]. Together these observations could suggest that PD could indicate a potential risk of developing severe COVID-19, since it has been closely associated with comorbidities like diabetes and asthma.

HIV (human immunodeficiency virus)

Patients with HIV or a compromised immune function, represent a group at higher risk of systemic and oral manifestations [91,92]. PD associated with HIV has been studied by several researchers [93–95], this possible association has been considered since PD is a source of chronic inflammation [96]. Some authors suggest that HIV is a contributing factor in the prevalence of PD. However, results have been inconclusive, and the issue is currently controversial [96–98].

On the other hand, HIV has been considered a risk factor for COVID-19 infection [99]. Early reports suggest that HIV patients are no more at risk than a non-HIV patient [100]. There are not enough studies yet, but it is believed that the degree of immunosuppression may contribute to a higher susceptibility to SARS-CoV-2 infection [101].

Cancer

Cancer is a malignant neoplasms disease driven by mutations that cause changes in the genome of normal cells. These mutations are consequence by exposition to chemical, physical, or environmental agents [102–104]. In recent years, PD has been identified as a risk factor that increases the development of cancer [105]. This fact has provided valuable information in researches on head and neck cancer [106], prostate cancer [107], breast cancer [108,109], lung cancer [110,111] and hematological cancer [112].

There is no enough evidence about specific mechanisms of interaction among cancer and PD. In this respect, several studies have already shown how dysbiosis induces inflammation, systemic translocation of periodontal pathogens through the weakened periodontal epithelium, systemic immune dysregulation, and the increase in circulating cytokines and chemokines [113–116]. According to several studies, inflammation can be promoted by microorganisms that increase the risk of developing cancer [117,118].

Patients with cancer are more susceptible to developing severe COVID-19 illness in large part owing to the presence of another comorbidity or risk factor [119–121].Therefore, their immune response is suppressed by treatments and nutritional deterioration, which in turn induces dysbiosis breakdown and increases the possibility of respiratory infections [122]. Patients with lung cancer are more likely to develop complicating COVID-19 [123]. Thus, identifying cancer patients with PD could represent a group at risk for severe COVID-19.

Oral Dysbiosis

Oral dysbiosis is the loss of the homeostatic balance of the oral microbial communities with the host, and it has associated with oral diseases like as PD [21,30,38]. The main pathogens associated with PD are *Porphyromonas gingivalis*, *Tanerella forsythia*, and *Treponema denticola* (red-complex), but there more pathogenic bacteria including species of the genera *Prevotella*, *Desulfobulbus*, and *Selenomona* as well as *Aggregatibacter* and others [30,38,124]. Host factors such as diet and immune system are determinant by the emergence and persistence of dysbiosis that allows the growth of pathobionts and their virulence

factors in PD [38]. Microbial communities execute a mechanism named "polymicrobial synergy and dysbiosis" that allows interaction between bacteria to become a dysbiotic community, where pathobionts grow and stimulate inflammation and tissue damage. Successfully, these pathobionts escape from epithelial barriers and an immune over-response of the host through mechanisms such as manipulation of neutrophils, inhibition of macrophage response, or subversion of complement [19].

On the other hand, in severe COVID-19 illness was reported that hospitalized patients with intubation or some life-saving invasive mechanism impaired their oral health. Also, there are other risk factors like the use of drugs routinely or experimentally to attack the SARS-CoV-2 virus, lack of oral hygiene, and other comorbidities that can produce dysbiosis of the oral microbiota that could trigger oral diseases like periodontal disease [15,20,125]. Within a metagenomic analysis of patients with severe COVID-19 illness has reported the emergence of genera *Prevotella*, *Fusobacterium*, *Veillonella*, which are associated with periodontal disease [20]. Additionally, some researches suggesting that the virus recognizes the ACE-2 receptor, which is localized in the nasopharynx but in oral mucosa too [50]. Therefore, the entry of the virus can subvert the immune system, and oral microbiota of host triggering a dysbiosis that allows a superinfection, understanding of the association of the PD with severe COVID-19.

Liver diseases

Association has been found between PD and liver diseases (LD). As they are, liver cirrhosis (LC), hepatocellular carcinoma (HCC), and Non-alcoholic Fatty Liver Disease (NAFLD) with a prevalence of 20–30% around the world. Even liver transplantation (LT) is associated with PD, since to avoid sepsis by periodontopathogens the patient has to be examined by an oral professional before LT [126–129]. Structural components and products of subgingival microbiome stimulate inflammation of periodontal tissues generating cytokines (IL-1β, IL-6, IL-10, IL-12, and TNF-α and INF-γ) [130] that are involved in the progression of liver diseases. Also, the lipopolysaccharide from *Porphyromonas gingivalis* induces liver inflammation [131].

Liver injury by SARS-CoV-2 is associated at the time of infection occurs and post treatment [132]. Although, it is considered that pre-existing LD patients would be more vulnerable to severe COVID-19 because the novel coronavirus binds hepatocytes and cholangiocytes using the ACE-2 receptor [133]. Thus, patients with liver diseases and PD could help to identify a group at risk for severe COVID-19.

Rheumatoid Arthritis

According to the WHO, rheumatoid arthritis (RA) is a chronic inflammation and disabling disease that affects the joints and connective tissues among other tissues. The prevalence ranges from 0.3 to 1%. Several studies reveal that relation between RA and PD exists [134,135]. Meta-analysis studies show that people with RA get worse when they have PD [136]. The molecular mechanism is not entirely clear. However, a member of the red complex *Porphyromonas gingivalis* is known to produce an enzyme that causes citrullination [135], and periodontal bacteria have been isolated from synovial fluid [134,137].

Nowadays, the main concern of rheumatologists in front of COVID-19 pandemic is the vulnerability [138] to SARS-CoV-2 of their patients with RA (which is an inflammatory disease) because it has been reported that patients with RA have twice the risk of infectious diseases and it also increases mortality when there is bronchopulmonary infection [139]. On the other hand, they are calm and have had experience in the management of certain medications such as chloroquine and hydroxychloroquine that they are using as a potential treatment for COVID-19 [140,141]. Closely association between PD and RA and possible inflammatory and bacterial underlying mechanisms could affect the outcome in patients with COVID-19.

Consequences of the hypothesis

There is enough evidence to propose that PD acts as a risk factor for COVID-19. PD has been widely associated with several disorders such as diabetes, HTA, obesity, among others. Thus, PD could be indicative of systemic health. Furthermore, these comorbidities and additional factors are common risk factors in patients with severe COVID-19 illness. Since periodontal health status has not been assessed in patients with COVID-19 illness, it is difficult to determine this association. However, it is possible that inflammatory, microbial and environmental factors could be implicated. It has been suggested that inflammatory factors could play important roles in the association of PD with comorbidities. In this sense, dysregulated inflammatory response also has been observed in severe COVID-19 illness contributing to its progression.

Alterations in oral microbial communities can affect the microenvironment with increases in pathogens and over-stimulation of the immune system [38]. Co-infection of pathobionts and the SARS-Cov-2 virus with established risk factors and comorbidities may play a role in increased inflammatory response and cytokine storm [142]. On the other hand, researchers suggest that exists a close relationship between lung microbiota and admission to intensive care. Patients have required ventilators for complications associated with bacteria belonging to gut microbiota not commonly found in the lung ecological niche. Therefore, there is a proposal to identify patients with initial gastrointestinal symptoms, since that could help predict patient outcomes and help to improve decision making relating preventive measurements and appropriate treatment. Consequently, it would be useful to characterize the microbiome in PD patients with COVID-19.

Even though some of the reported risk factors have not been strongly associated with PD or their causal relationships are not completely established, it is convincing to propose an association between PD and COVID-19, where the latter could be affected by the intervention of periodontopathogenic bacteria outside its ecological niche and cause chronic inflammation. Additionally, it is possible that the association between PD and severe COVID-19 illness could be non-causal, suggesting that prevention or treatment of PD does not prevent a worse progression and outcome of COVID-19. Future studies on the periodontal status of patients with COVID-19, including from mild to severe forms, could allow the opportune identification of people in risk of severe illness, and generation of relevant recommendations.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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