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## ARTIGO DE REVISÃO

### Can COVID-19 in critically ill patients be aggravated by periodontal disease?

*O COVID-19 em pacientes gravemente doentes pode ser agravado por doença periodontal?*

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**Abstract:** This article addresses, through a literature review, the biological and immunological plausibility of the relationship of pro-inflammatory mediators of periodontal origin with the worsening of the clinical condition of patients with COVID-19 in critical condition. Periodontal disease is a pathology that is directly related to the various possibilities of systemic changes due to pro-inflammatory mediators, cytokines that also act in COVID-19. There is a biological and immunological scientific plausibility of the action of pro-inflammatory mediators of periodontal origin in the individual's body, however, in critical patients with COVID-19, more research is needed to elucidate this relationship.

**Keywords:** Coronavirus. COVID-19. Periodontal disease. Dentistry.

**Resumo:** Este artigo aborda, por meio de revisão bibliográfica, a plausibilidade biológica e imunológica da relação dos mediadores pró-inflamatórios de origem periodontal com o agravamento da condição clínica de pacientes com COVID-19 em estado crítico. A doença periodontal é uma patologia que está diretamente relacionada às diversas possibilidades de alterações sistêmicas devido aos mediadores pró-inflamatórios, citocinas que também atuam no COVID-19. Há uma plausibilidade científica biológica e imunológica da ação de mediadores pró-inflamatórios de origem periodontal no corpo do indivíduo, porém, em pacientes críticos com COVID-19, mais pesquisas são necessárias para elucidar essa relação.

**Palavras-chave:** Coronavirus. COVID-19. Doença periodontal. Odontologia.

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## INTRODUCTION

Coronaviruses are viruses which contains a large, single-stranded, and enveloped RNA, and they can not only infect humans, but also a wide variety of animals (VELAVAN and MEYER, 2020). Due to the new coronavirus, the World Health Organization (WHO) has recommended the use of the disease name as COVID-19 and the virus as SARS-CoV-2 by the International Virus Taxonomy Committee. (YUEN et al., 2020).

The etiopathogenesis of COVID-19 can be explained by the binding of the SARS-CoV-2 virus S2 protein (Spin Protein) with the host cell receptor as the angiotensin-converting enzyme 2 (ACE2) that fuses with the cell membrane of the host, and initiates the viral cycle. Severe cases have shown respiratory, gastrointestinal and neurological complications that can lead to mortality. (BALAMURUGAN et al., 2020).

The average period for the appearance of the symptoms of COVID-19 is about 5.2 days and the increase in the levels of pro-inflammatory cytokines such as interleukins and tumor necrosis factor- $\alpha$  (TNF  $\alpha$ ) is the reason for the increase of the severity of the disease in critically ill patients. (ROTAN and BYRAREDDY, 2020).

These patients can often suffer from periodontal diseases (PD), since they affect 90% of the world population. Among these PD, the mildest form is gingivitis, which is characterized by inflammation of the gingival tissue around the teeth caused by the accumulation of biofilm, which does not affect support structures (PIHLSTROM, MICHALOWICZ and JOHNSON, 2005). However, periodontitis involves the destruction of bone tissue, periodontal ligament and collagen fibers, and all of these structures act in support of the tooth to the alveolar bone (MYATA et al., 2019). The condition of gingivitis is reversible, however, the destruction of supporting tissues caused by periodontitis is irreversible, which can lead to tooth loss (PIHLSTROM, MICHALOWICZ AND JOHNSON, 2005; TADA and MIURA, 2017).

These diseases occur due to the imbalance between the microbial community and the host, leading to dysbiosis, or inflammatory response exacerbated by the host (KINANE, STATHOPOULOU and PAPANOU, 2017). Thus, patients with periodontal disease have frequent exacerbated inflammatory responses (KANG, HU and GE, 2016), and it is known that these are aggravating factors for pathologies and comorbidities that a patient may present.

On the basis of the above, the objective of this work is to evaluate, through a literature review, the biological and immunological plausibility of the relationship between pro-inflammatory mediators of periodontal origin with worsening of the patient's clinical condition with COVID-19 in the clinical state.

## MATERIALS AND METHODS

A literature review was carried out on SARS-CoV, SARS-CoV2, COVID-19 published in 2020 and on periodontal disease, pregnant women,

arteriosclerosis, atheroma plaque, diabetes, premature birth, inflammatory modulation, pro-inflammatory cytokines from 1996 to 2020 The abstracts and titles of articles published in the PubMed database in the last 25 years (1996 to March 2020) and books published in the Brazilian ISBN Agency were analyzed, with the keywords: periodontics, hospital dentistry (2018 to 2020).

The inclusion criteria were considered as a study to assess the association between inflammatory mediators, systemic changes, respiratory disease, pneumonia, heart disease, arteriosclerosis, premature birth, COVID-19 and as exclusion criteria, scientific articles that did not have an association between inflammatory mediators, systemic changes, respiratory disease, pneumonia, heart disease, arteriosclerosis, premature birth and hospital dentistry as the objective of the work.

## RESULTS AND DISCUSSION

Kit-San et al. (2020), stated that the main cause of the pathogenic inflammation of COVID-19 is the induction of a cascade of cytokines, suggesting the comparison of SARS-CoV and SARS-CoV-2 viral proteins for their ability to modulate pro-responses. inflammatory.

Among the host's responses to the virus, there are reports of increased levels of inflammatory markers with C-reactive protein and pro-inflammatory cytokines (VELEVAN and MEYER, 2020). Yan-Rong Guo et al. (2020), cited arterial hypertension, chronic obstructive pulmonary disease, diabetes and heart diseases as risk factors for the worsening of COVID-19, associating the increase in inflammatory factors such as interleukins, tumor necrosis factor- $\alpha$  and C-reactive protein with the aggravation of the disease. They also pointed out that treatment with test medications such as chloroquine suppresses the levels of these inflammatory mediators.

Periodontal disease is an inflammatory pathology in response to the aggression of bacterial metabolites that do not produce biofilm, therefore, there is the release of chemical substances from chemicals by individuals that cause periodontal disease and it is directly related to several social variables.

Could the pro-inflammatory cytokines from periodontal disease be added to those produced by COVID-19 and aggravate the patient's clinical condition?

With this inflammatory characteristic of periodontal disease, cytokines can reach the bloodstream and produce their effects systemically. The exact determination of the minimum amount of these substances needed to trigger systemic changes is unknown; what is known is the greater involvement of more extensive and serious periodontal diseases as a risk factor when compared to milder situations or periodontal health.

A hypothetical situation to exemplify could filling a water tank with a dropper. This might take a long time, but at a certain point, a single drop can cause an overflow. Analogically, this same situation occurs in

the human organism, where perhaps a certain amount of cytokines caused by a less aggressive periodontal disease does not cause relevant clinical changes systemically, while a more aggressive periodontal disease can initiate unwanted changes in the organism. The extremes are easily understood, however, the situations interposed require further studies to elucidate the minimum necessary of these substances to develop systemic changes (RORIZ and RORIZ 2018).

The cytokines generated by periodontal disease and their systemic relationships have been shown in patients with diabetes, where the first causes the serum levels of C-reactive protein and biomarkers of oxidative stress to rise, and the presence of these components in the bloodstream makes control difficult. glycemimetic (FAGGION; CULLINAN and ATIEH, 2016). These substances (cytokines) antagonize the action of insulin, thus promoting the maintenance of hyperglycemia (COSTA, JUNIOR and RÊGO, 2009).

In addition, hyperglycemia, the main characteristic of diabetic individuals, induces an increasing accumulation of products of glucose degradation in plasma and tissues, while these products bind to cell receptors such as macrophages, initiating a cycle of supra regulation of inflammatory cytokines, an exacerbation of periodontal disease occurs (IZU et al., 2010).

In contrast, periodontal treatment and oral hygiene reduce glycated hemoglobin levels by up to 80 percent, in addition to lowering levels of inflammatory mediators in half, agents that cause insulin resistance (CORREIA, ALCOFORADO and MASCARENHAS, 2010; COSTA, JÚNIOR and RÊGO, 2009), however, there is a consensus among several authors about the control of therapy, improvement of periodontal condition and metabolic control of the disease (ALDRIDGE, 1996).

Another explanation about the relationship between periodontal disease, systemic changes and the role of inflammatory mediators occurs in the formation of arteriosclerosis, which is a change in the permeability of the blood vessel wall, with the entry of lipids and inflammatory cells into the arterial wall, causing the atherosclerotic plaque. The result is the inability of the endothelium to respond adequately to systematic attacks (TOREGANI et al., 2014).

Similarly, in pregnant patients, periodontal diseases can act for childbirth to occur before the expected time for two reasons: the pro-inflammatory cytokines resulting from periodontal diseases reach the bloodstream to the amniotic fluid, increasing the levels of prostaglandins, interleukins, a factor tumor necrosis and C-reactive protein, confusing the organism and initiating the delivery process, or bacteria of oral origin settle in the placental tract, promoting inflammation and release of cytokines in that location. Therefore, studies point to periodontal disease as a risk factor to the individual's general health and relate to an association between premature birth and low birth weight (OFFENBACHER et al., 1998; GLESSE, 2004; MOKEEM, 2004; LOPES, 2005; GOMES et al. 2009; NAVES, 2009).

The relationship between pneumonia associated with mechanical ventilation (MVAP) and periodontal disease is well known in the scientific community, especially in patients admitted to intensive care units. MVAP is one of the most prevalent hospital infections in intensive care units (ICU), with rates ranging from 9% to 40% of infections acquired in this unit, and it is associated with an increase in the period of hospitalization and mortality rates, which are estimated between 20 and 50%, and causes a significant impact on hospital costs (AMERICAN THORACIC SOCIETY, 2005; RUFFELL and ADAMCOVA, 2008; TANTIPONG et al., 2008; BERALDO and ANDRADE., 2008; MUSCERERE, 2008; ANCHABHAI et al., 2009 ; MUNRO et al., 2009; KALANURIA et al., 2014).

The oral cavity becomes a reservoir of respiratory pathogens that can initiate a pulmonary inflammatory response with consequent formation of inflammatory exudate (FERNANDES and ZAMORANO, 2000). Theoretically, there is a direct contribution in the formation of cytokines, through the infection of bacteria of oral origin in the lung, and also an indirect contribution of inflammatory mediators of the oral cavity, originating from periodontal disease, through hematogenous transmission to the lower respiratory tract, but it is unknown the impact of this increase on the clinical state of critically ill patients with COVID-19.

## CONCLUSION

There is biological and immunological plausibility of the action of pro-inflammatory mediators of periodontal origin in the host's body, however, in patients with COVID-19 in critical condition, further studies are needed to elucidate this relationship.

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