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REVIEW ARTICLE

Relationship of periodontitis and Covid-19 in patients suffering from systemic comorbidities

Relación de la periodontitis y Covid-19 en Pacientes que sufren comorbilidades sistémicas

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ABSTRACT

Introduction: periodontal disease is an infectious and inflammatory condition, and its development and severity involves local factors such as biofilm and systemic factors specific to the host.
Objective: to argue the relationship between periodontal disease and complications in patients with comorbidities and COVID-19.
Methods: a narrative literature review was carried out using the Google Scholar search engine in databases such as Clinicalkey, Pubmed, Scielo, Medigraphic. Inclusion criteria were: studies from the last five years, epidemiological studies, observational studies in patients. Exclusion criteria: studies older than five years, monographs, literature reviews, studies not performed on humans.
Results: the literature consulted indicates that there is a direct relationship between COVID-19 and the severity of periodontal disease in patients with comorbidities such as diabetes, hypertension or cardiovascular disease, and obesity, among others. During the course of the pandemic, there were significant findings of oral manifestations in patients with COVID-19, and it also plays an important role in virus entry and transmission.
Conclusions: oral health plays an important role in the prevention and eventual complications due to COVID-19, taking into account the systemic risk factors that could lead to aggravate the disease.

Keywords: Periodontitis; Systemic Disease; Comorbidity; Cardiovascular Diseases; Obesity.

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RESUMEN

Introducción: la enfermedad periodontal es un padecimiento infeccioso e inflamatorio, implica para su desarrollo y gravedad, factores locales como el biofilm, y sistémicos propios del huésped.
Objetivo: argumentar la relación entre la enfermedad periodontal y las complicaciones en pacientes con comorbilidades y COVID-19.
Métodos: se realizó una revisión bibliográfica narrativa realizada a través del motor de búsqueda Google Académico en bases de datos como *Clinicalkey, Pubmed, Scielo, Medigraphic*. Los criterios de inclusión fueron: estudios de los últimos cinco años, estudios epidemiológicos, estudios observacionales en pacientes. Los criterios de exclusión: estudios que sobrepasen los cinco años de antigüedad, monografías, revisiones bibliográficas, estudios no realizados en humanos.
Resultados: la bibliografía consultada indica que existe una relación directa entre el COVID-19 y la gravedad de la enfermedad periodontal en pacientes con comorbilidades como por ejemplo de la diabetes, hipertensión o enfermedades cardiovasculares, y la obesidad entre otras. En el transcurso de la pandemia se observaron importantes hallazgos de manifestaciones orales en pacientes con COVID-19, además tiene un papel importante en la entrada del virus y su transmisión.
Conclusiones: la salud bucodental juega un papel importante en la prevención y eventual complicaciones por COVID-19 tomando en cuenta los factores de riesgo sistémicos que podrían llevar a agravar la enfermedad.

Palabras clave: Periodontitis; Enfermedad Sistémica; Comorbilidad; Enfermedades Cardiovasculares; Obesidad.

INTRODUCTION

Periodontal disease is one of the most common oral diseases worldwide and specifically when talking about periodontitis we know that it is a chronic inflammatory condition that affects the supporting tissues of the tooth.[1,2]

With the advent of the global health emergency of SARS-CoV-2 responsible for the coronavirus disease COVID-19.[1] Several studies refer to the fact that different findings have been found with which these two diseases share risk factors and become more dangerous or have serious consequences when the individual is systemically compromised.[3]

The different findings have linked COVID-19 and the severity of periodontal disease in patients with comorbidities such as Diabetes Mellitus, high blood pressure, cardiovascular diseases, and obesity, among others.[2]During the course of the pandemic, important findings of oral manifestations have been observed in patients with COVID-19, in addition to having an important role in the entry of the virus and its transmission.[4,5]

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The relationship between these two diseases is the result of the increased expression of several inflammatory mediators, such as interleukins, tumor necrosis factor, prostaglandins, C-reactive protein, in addition to the bacterial etiological factor to which periodontitis is linked, periodontal pathogenic bacteria have been detected in the bronchoalveolar lavage fluid of patients with COVID-19, in addition to the periodontal pockets acting as a viral reservoir. There is also an increase in the expression of the angiotensin converting enzyme *E2*, promoted by bacteria, which increases the infection rate of SARS-CoV-2.[6]

This association is more present in people who have more severe Periodontitis, where there is more bone loss around the teeth due to the exacerbation of the cytokine response, especially IL-16 and tumor necrosis factor, showing similarity with people with severe coronavirus infection, on the contrary, the oral manifestations of people who have much milder and moderate forms of periodontal disease, the oral manifestations are not evident.[7]

Patients who present positive signs of coronavirus infection also present a wide variety of oral lesions mainly in the tongue, palate, lip, mucosa and gums, including depapillation of the tongue, angular cheilitis, some studies suggest two types of lesions, the first similar to aphthous ulcers in young patients, secondly, herpetic ulcers that extend through the oral mucosa appear in older individuals, and with a certain degree of immunosuppression. As well as facial pain, oral submucosa, persistent burning of the mouth and xerostomia.[8,9]

Inflammatory and immune response of periodontal disease and COVID-19

The inflammatory process that occurs in Periodontitis is associated with the inflammatory response produced by covid-19 due to the elevation of cytokine expression could cause greater damage to dental supporting tissues and increase the worsening of the prognosis of patients with COVID-19 infection.[10,11] This overproduction of cytokines is also called "cytokine storm" which will be characterized mainly by increased levels of various interleukin (IL-1), IL-6, IL-17, among the main ones also TNF-alpha, MIP-1A, MIP-1B, MCP-1 and IP-10, which causes tissue damage. The secretion of cytokines produces an inflammatory infiltrate where the response of B and T lymphocytes is not adequate or is affected against bacterial components contributing to the chronic systemic inflammatory response.[12]

In general, the oral mucosa is known to be an important reservoir of pathogens since the The oral cavity is an important reservoir of pathogens since SARS-CoV-2 lodges in the oral cavity and is present in large quantities in saliva. These patients are more susceptible to the correlation between these two diseases, also due to the overexpression of the ACE2 and Cd147 receptors involved in the entry of the coronavirus into the host. ACE2 receptors in respiratory epithelial cells and proteases derived from periodontopathogens are increased, increasing and activating protein S, causing its pathogenicity.[13]

The changes that the composition of dental biofilm can undergo due to pathogenic microorganisms, that is, dysbiosis, can result in an increase in periodontopathogens. Therefore, patients with COVID-19 are more prone to oral dysbiosis, where there will be a deterioration in the immune response, either due to medications or changes in the type of diet. In critically ill hospitalized patients, these periodontopathogens will constitute a pro-inflammatory stimulating component for the lower respiratory tract. In addition, pulmonary hypoxia would stimulate the growth of anaerobic bacteria from the oral microbiota.[14]

For this reason, several studies suggest that this change in the oral microbiota as a result of oropharyngeal colonization is the main pathophysiological mechanism for the development of ventilator-associated pneumonia in patients intubated by the virus.[15]

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Patel suggests, based on the latest findings, that there is a particular prevalence of necrotizing periodontal disease and patients confirmed to have COVID-19 infection, which may be associated with bacterial co-infections due to metagenomic mapping performed on patients diagnosed with the virus, resulting in increased readings of certain bacteria predominant in acute infections such as Prevotella intermedia, Fusubacterium, Treponema, and Veillonella.[16]

Comorbidity of COVID-19 and periodontitis

The bidirectional existence of the prevalence of periodontal disease and systemic diseases has been reported quite clearly. In patients with systemic diseases, there is a high prevalence of contagion and severity of infection by the Covid-19 coronavirus, there could be an existing comorbidity as a risk factor in patients with Periodontitis.[14,17]

Among the most relevant systemic diseases where significant suspicions of a relationship have been found, we have cardiovascular diseases, hypertension, diabetes, obstructive pulmonary disease, obesity and smoking. We will take into account that the evidence and epidemiological studies indicate that periodontal disease presents an inflammatory response that not only reaches a local level but also a systemic one.[18,19]

Since Periodontitis is a chronic disease with periods of exacerbation, certain types of molecular mechanisms are involved that modulate the host's immune response to bacterial exposure, because these systemic conditions share several risk factors that relate both conditions.[20,21]

Aging

It has been reported that older adult patients whose aging process is subject to degenerative changes at the cellular level, the WHO considers that this is a considerable risk group because it will be common for these patients to present risk factors such as poor oral hygiene in addition to the presence of chronic diseases, use of medications, lack of any dental treatment where the oral microbiota can allow the development of periodontal disease, respiratory infections, constituting a rapid attack factor for the COVID-19 virus and increasing the mortality of patients over 65 years of age. Also due to a critical factor since the immune response is not as strong compared to young patients.[22,23]

Therefore, aging will determine a risk factor in the link between periodontal disease and COVID-19 since they share risk factors that could lead to complications in response to the disease.

Gender

It has been suggested through different studies that men may be more prone to acute and more severe periodontal diseases such as necrotizing ones in which they could be associated with the immune difference, environmental and behavioral factors, however, this is not well determined and similarly it was suggested that men are more likely to develop severe cases of COVID-19 coronavirus infection due to the immune response in which case the evidence suggests that periodontal disease could be accelerated considering its association with COVID-19 with gender and immunological factor.[24]

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Diabetes Mellitus
Scientific evidence indicates that there is a bidirectional relationship between the development of periodontal disease and diabetes. This is because periodontal disease can cause uncontrolled blood sugar levels and, in turn, having diabetes increases the possibility of developing periodontitis. It is explained that the mechanisms that occur in this association may be alterations in processes such as tissue repair, vascular, cellular and changes in the host response. The evidence in the studies provided indicates that patients with COVID-19 have an affected expression of the angiotensin-converting enzyme 2 in the lungs.

This receptor is highly expressed in diabetics due to pharmacological treatment with ACE inhibitors and angiotensin receptors. In addition, both in periodontal disease and in patients who are positive for COVID-19, the immune response will be affected by various external and internal host factors.

High blood pressure and cardiovascular diseases
There are several epidemiological studies that have shown the association between periodontal disease, hypertension and cardiovascular diseases.

Because their association occurs because in periodontal disease the accumulation of several species of bacteria in bacterial plaque or dental biofilm induces a chronic inflammatory expression specifically by inducing the production of cytokines that also cause an increase in C-reactive protein CRP being this a marker of cardiovascular disease and hypertension therefore in periodontitis the presence of C-reactive proteins is considered the link between these diseases. In addition, by having the migration of periodontopathogens through the vascular walls towards coronary structures.[21]

Other studies indicate that ACE2 could be expressed in oral mucosa cells, therefore its expression in hypertension and periodontal disease represents a risk factor for COVID-19.[23]

Obesity
Study models indicate that obesity can alter the periodontal microbiota, substantially increasing bacterial growth in the mouth. Obesity is a state of systemic inflammation, causing the release of cytokines such as adipokines, including leptin, which can contribute to the development of periodontitis by altering the response and aggravating damage to gingival tissues. Obesity increases the risk of complications in patients with COVID-19. Periodontitis increases the systemic inflammatory response by disseminating bacterial products that cause periodontal disease, mainly cytokines in patients with the virus, thus altering their immune response and therefore generating a higher risk of complications.[22]

METHODS

This research is a narrative bibliographic review carried out to argue the relationship between chronic periodontitis and COVID-19 and its influence on comorbidities of patients with systemic diseases. The Google Scholar search engine was used to locate databases such as: Clinicalkey, Pubmed, Scielo, Medigraphic. The inclusion criteria were: studies from the last five years, epidemiological studies, observational studies in patients.

Exclusion criteria were studies older than five years, monographs, bibliographic reviews, and studies not conducted on humans. Studies that met the inclusion criteria were analyzed and a summary was designed explaining the relationship that exists.

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RESULTS

Author	Aim	Results	Conclusions
Marouf N et al [5]	Association between COVID-19 and periodontitis demographic characteristics and associated medical factors.	568 patients were analyzed in which comorbidity of systemic diseases and their relationship with periodontitis were adjusted, increasing the risk of ending up in an ICU in patients with COVID-19.	Periodontitis was associated with a higher risk of reaching an ICU and the need for assisted ventilation and death due to COVID-19 and the association with other biomarkers of associated systemic diseases.
Garcia M et al [3]	Well-recognized association between periodontitis and systemic diseases. The role of periodontitis in the severity of COVID-19.	Severity and mortality risk depend of factors such as age, gender and presence of any comorbidity such as hypertension, diabetes, disease heart disease and obesity,	Both the SARS-COV-2 infection and the prognosis and worsening of the clinical picture are influenced by the oral status in many aspects of the disease, indirectly or directly, causing additional systemic complications.
Alves C et al [2]	Systemic comorbidities and periodontitis	High incidence of severity in hospitalized patients who presented a large presence of dental biofilm.	Presence of dental biofilm as an important aspect in the appearance of periodontal disease increases the risk in patients with systemic diseases, increases the severity of the disease and exacerbates the inflammatory storm

DISCUSSION

Regarding the evidence, it has been shown that patients with COVID-19 who have diseases such as diabetes, kidney problems, heart disease, obesity and also due to the exchange and increase in dental biofilm in patients with periodontitis, which provides the appropriate environment for the vehicle of respiratory pathogens, are related to the presence of greater complications related to COVID-19 in a systemic way.

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There is a significant association between periodontal disease, mainly periodontitis, with COPD and pneumonia, either by aspiration, which is generally direct, of oral pathogens into the lungs or by damage or alteration of the respiratory tract mucosa, where cross-infection may occur due to adhesion and invasion of periodontal pathogens.[3]

Several authors agree that the oral cavity acts as a reservoir of the virus responsible for COVID-19 because periodontal pockets such as dental biofilm are ideal environments for not only bacterial but also viral growth, being a community and environment where these species can proliferate.[5,6]

Systemic diseases constitute that factor that can cause exacerbation of the inflammatory response and since periodontitis is a chronic inflammatory disease, it constitutes the reason for this relationship that exists, in addition to the fact that periodontitis pathogens induce the release of proinflammatory products such as cytokines that play an important role in the destruction of periodontal tissues as well as in the respiratory and pulmonary tract that occurs in COVID-19, increasing the risk of complications and hospitalization due to respiratory problems.[10,11]

There are various factors that can define this correlation of increased viral replication, dysbiosis or changes in the structure of bacterial plaque, exacerbation of increased inflammation due to immune disorders, and associated chronic diseases.[24]

The evidence and epidemiological studies given in the years of the pandemic suggest that the presence of the virus in the mouth, in the oral mucosa including saliva and periodontal tissues correlate with viral entry and causes oral manifestations in these patients, therefore, we must pay special attention to the oral examination in order to act in a more appropriate manner.[24]

CONCLUSIONS

Chronic periodontitis does represent a risk factor for complications of COVID-19 infection, taking into account that there are vulnerable groups such as systemically compromised patients who may develop an unfavorable evolution and a higher risk of complications from SARS-CoV-2 infection. There is a close relationship with these entities in which most comorbidities and associated factors can aggravate the development and speed of onset of periodontal disease.

Declaration of conflict of interest
The authors declare that there are no conflicts of interest.

Authors' contributions
All authors participated in conceptualization, data curation, formal analysis, investigation, methodology, supervision, writing-original draft, writing-review, and editing.

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