Review

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Abstract: Inflammation plays a fundamental role in the development and bidirectional association of diverse diseases, such as periodontitis and type 2 diabetes mellitus, which generates important clinical complications, where chronic exposure to high levels of blood glucose affects the repair process of periodontal tissues. Likewise, it has been observed that comorbidity, between these two diseases, influences the development of the COVID-19 disease towards a more severe course. However, there is currently very little scientific evidence on the relationship between periodontitis, type 2 diabetes mellitus and COVID-19 disease. This narrative review aims to provide an understanding of the current and most relevant aspects of the relationship between periodontitis, type 2 diabetes mellitus and COVID-19 disease. A narrative review was performed through a systematic search of published studies, without date restrictions, indexed in the electronic databases of PubMed, for the inclusion of articles in English, and LILACS for the inclusion of articles in Spanish. This review included different articles, which addressed the most important aspects to present a current perspective on the relationship and influence between periodontitis, type 2 diabetes mellitus and COVID-19 disease. Comorbidity between periodontitis and type 2 diabetes mellitus represents a greater risk of developing a more severe course of COVID-19 disease, because these three diseases share three important axes: a clinicopathological axis; an axis associated with glycemia, and an immunological axis associated with inflammation.

Keywords: COVID-19; inflammation; periodontitis; SARS-CoV-2; type 2 diabetes mellitus

1. Introduction

At a clinical level, periodontal health is characterized by the absence of inflammation [1]. Under these conditions, the periodontal tissue is capable of adequately defending itself, through various mechanisms of the immune system, against the presence of bacteria present in the oral cavity. Periodontal disease develops when the balance between these defense mechanisms that control infection and the subgingival biofilm is lost, triggering the innate (inflammation) and adaptive immune response of the host [2]. Periodontal disease can be divided into four stages based on the type of lesion: 1) initial and 2) early lesions; which are part of gingivitis; and the 3) established and 4) advanced lesions that are part of periodontitis [3]. In this context, periodontitis is an

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immunoinflammatory disease that mainly affects the periodontal tissues that support the teeth, causing their progressive destruction, which ultimately results in tooth loss [4]. On the other hand, there are risk factors that influence the development and severity of periodontal disease, which can be local and systemic. Likewise, these factors can also be modifiable, such as smoking, stress, obesity, and uncontrolled diabetes mellitus, among others; and non-modifiable such as sex, age, ethnicity or genetic factors [5].

Diabetes mellitus is a syndrome that involves a wide variety of genetic, epigenetic and pathophysiological abnormalities, which can be influenced by environmental factors, such as infections, diet (nutrients), intestinal microbiota, among others [6–9]. Type 2 diabetes mellitus (T2DM) is the most common type of diabetes. T2DM is characterized by presenting various defects at a biochemical and pathophysiological level, which are associated with peripheral insulin resistance, increased hepatic glucose production, altered levels of intestinal hormones that regulate insulin and glucagon function, decrease and failure of pancreatic β cells function, as well as additional mechanisms that are related to inflammation [10–12].

Several studies have associated T2DM with periodontitis, suggesting a bidirectional association between both pathologies [13,14], since patients with T2DM have a greater probability of developing periodontitis, and in those patients who present this comorbidity, between both pathologies, they show worse blood glucose control [15–17]. In this context, T2DM leads to an increase in the expression of proinflammatory cytokines in periodontal tissues [18], such as interleukin (IL)-1β and prostaglandin (PG)-E_2 in gingival crevicular fluid. Likewise, an increase in the expression of tumor necrosis factor (TNF)-α, IL-1β, IL-6, IL-17, and IL-23 in the gingiva has been reported, both in patients and in animal models with diabetes [19,20], which influences the vascular and cellular phenomena of inflammation [21], stimulating greater bone resorption, through an increase and reduction in the expression of the receptor activator of nuclear factor-κ B ligand (RANKL) and osteoprotegerin, respectively [22]. On the other hand, inflammation also induces an increase in the production and activation of matrix metalloproteinases, which leads to the destruction of connective tissue, induction of apoptosis in fibroblasts and osteoblasts, thus limiting the repair capacity of the periodontal tissues [23–25]. Furthermore, a decrease in the production of anti-inflammatory lipid mediators and cytokines such as IL-4, IL-10 and transforming growth factor (TGF)-β has been reported, potentially contributing to the development and aggravation of periodontal inflammation in patients with T2DM [26–28].

Another important factor during T2DM is the role of blood glucose concentration, since high blood glucose levels contribute to the development and evolution of inflammation, through the activation of various intracellular signaling pathways. For example, mitogen-activated protein kinase (MAPK) and nuclear factor (NF)-κB pathways, which results in an increase in the production of proinflammatory mediators, such as cytokines and reactive oxygen species [29–32]. Furthermore, it has been observed that patients with T2DM show an increase in both the expression of inducible nitric oxide synthase (iNOS) and the levels of lipid peroxides in the periodontium and crevicular fluid, respectively, which contributes to a more severe course of the periodontal inflammation [33].

The COVID-19 disease, caused by SARS-CoV-2, has caused alarming numbers of infections and deaths around the world [34]. The clinical characteristics of the COVID-19 disease are very diverse, which can present from an asymptomatic state, or mild symptoms can manifest [35]; until progressing to pneumonia, developing acute respiratory distress syndrome (ARDS), multiple organ dysfunction and death [36]. The pathophysiology of COVID-19 disease may not be limited exclusively to pulmonary manifestations, including pneumonia and ARDS [37], since SARS-CoV-2 is able to infect other cell types which express its binding receptor, angiotensin-converting enzyme (ACE)-2 [38], such as cells of the upper respiratory system, alveolar epithelial cells in lungs, enterocytes, endothelial cells [39], from heart [40], tubular epithelium kidney [41] and pancreas [42], causing organ-specific extrapulmonary clinical manifestations associated with harmful effects on many other systems of the human body, such as neurological, thrombotic, endocrine, cardiac, dermatological, hepatic, renal and gastrointestinal [37]. Although it is known that the majority of people with COVID-19 do not develop symptoms or only have mild manifestations of the disease,

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approximately 14% of infected people develop the disease with a severe course [43], where advanced age and some comorbidities, such as diabetes [44], have been associated as potential risk factors for triggering more severe disease and death [43]. Diabetic patients who suffer from COVID-19 have a prevalence of death between 22 to 31%, compared to patients without diabetes [45]. Elements that could influence in patients with diabetes mellitus to increase susceptibility to COVID-19 disease include: greater ease for the virus to adhere and efficiently enter cells, less effectiveness of the immune system in eliminating the virus, greater probability of suffering severe complications due to the excessive release of proinflammatory cytokines causing hyperinflammation, and presence of diseases associated with the heart [38]. Likewise, it has been shown that there is high expression of ACE2 in the lung, kidney, heart, and pancreas in rodent models of diabetes mellitus [46,47], and a higher pulmonary expression of ACE2 in humans [48]. In this context, diverse studies support the hypothesis that patients with diabetes mellitus have greater susceptibility to SARS-CoV-2 infection, since they are not able to efficiently eliminate the virus. This is due, on the one hand, to the fact that patients with diabetes mellitus have high levels of furin, a protease involved in cleaving the S1 and S2 domains of the virus spike protein, which facilitates the entry of the virus into the cell [49]. Furthermore, patients with diabetes mellitus present alterations in the immune system, which inhibit neutrophil chemotaxis, phagocytosis, and intracellular destruction of pathogens, as well as delaying both the activation of Th1 cells and the hyperinflammatory response [50,51]. On the other hand, patients with COVID-19 present, at a peripheral level, low counts of CD4+ and CD8+ T cells, but with a higher proportion of pro-inflammatory CD4+ Th17 T cells, along with high levels of pro-inflammatory cytokines [52].

Currently, there is not enough scientific evidence on the relationship between periodontitis and T2DM and the risk of SARS-CoV-2 infection. Therefore, a more extensive and exhaustive search is necessary to identify additional literature; and in this way provide a more reliable and accurate hypothesis and conclusion about the association of these three pathologies. In this context, the aim of this research was to provide a systematized narrative review to contrast the existing evidence on the relationship between periodontitis, T2DM and COVID-19 disease. In this narrative review, a systematic methodology was applied [53], without date restrictions, indexed in the electronic databases of PubMed, for the inclusion of articles in English, and LILACS for the inclusion of articles in Spanish, through the use of the Boolean operators AND, OR and NOT; using the following DeCS/MeSH terms: “periodontal disease”, “periodontitis”, “type 2 diabetes mellitus”, “SARS-CoV-2” and “COVID-19”.

2. Periodontitis and Type 2 Diabetes Mellitus

Periodontitis is considered the sixth complication of diabetes mellitus [26], because several studies have shown a strong bidirectional relationship between these diseases, since it has been observed that in subjects with T2DM (controlled or not) present a significant increase in the prevalence of chronic or severe periodontitis, compared to healthy subjects [54–59].

This bidirectional relationship between periodontitis and T2DM is also because both diseases share pathogenic inflammatory mechanisms (Figure 1). On the one hand, periodontitis can influence the development and state of chronic systemic inflammation, through the aberrant increase in proinflammatory cytokines, such as IL-1β, IL-6 and TNF-α, affecting endothelial function, and substantially contributing to the development of insulin resistance, causing a homeostatic imbalance in blood glucose regulation [60]. On the other hand, T2DM is closely related to vascular endothelial dysfunction, affecting the protective balance and permeability of the endothelium, enhancing chronic systemic inflammation [61–63].

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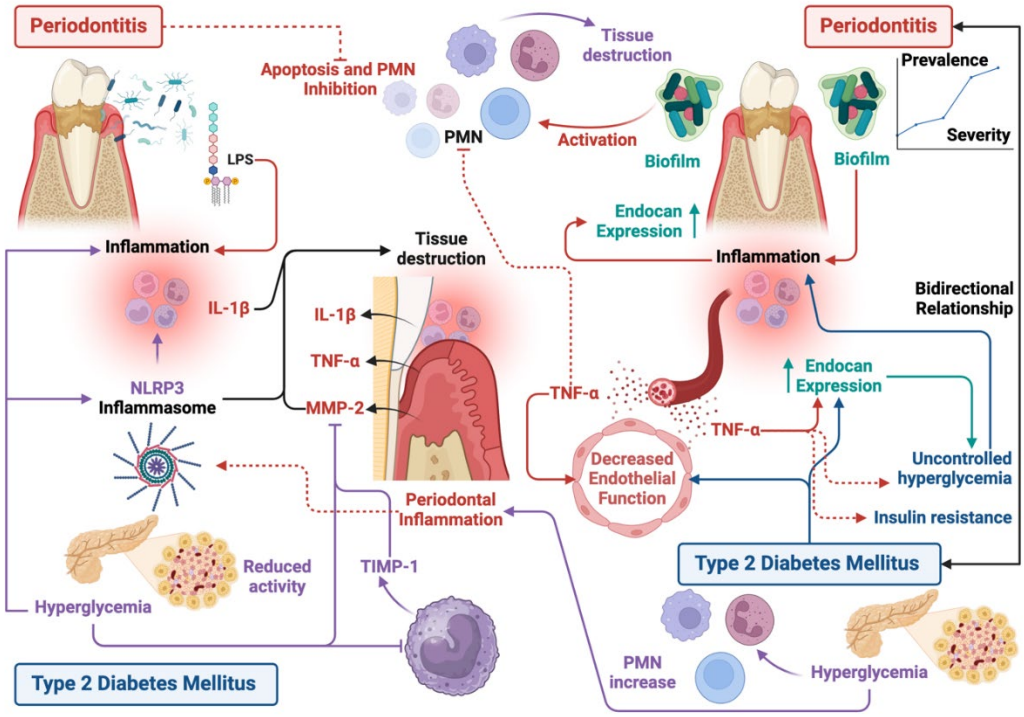

Figure 1. Pathogenic inflammatory mechanisms between periodontitis and type 2 diabetes mellitus. Explanation in the text. Figure created on Biorender.com by Muñoz-Carrillo et al.

TNF-α plays a crucial role in regulating the expression of endocan, a soluble proteoglycan that is highly produced by vascular endothelium during endothelial activation and inflammatory processes [64]. This dual characteristic allows that the endocan may act as both an inflammatory mediator and a marker of endothelial activation [65]. Interestingly, studies have shown a correlation between elevated endocan levels and worsening glycemic control; while improvements in glycemic control lead to a decrease in endocan expression. Furthermore, endocan expression has been detected in systemically healthy individuals with periodontal disease [66,67], suggesting a potential link beyond glycemic status. In this context, endocan could be a promising biomarker for the early diagnosis and prognosis of chronic inflammatory states in T2DM and periodontal disease, due to its ability to reflect the impact of endothelial activation in these pathological conditions. Furthermore, endocan could serve as an indicator for monitoring the response to treatment in patients with T2DM and periodontal disease, since the alteration of its levels is associated with the inflammatory state and glycemic control in individuals with these pathologies [68].

On the other hand, a hallmark of metabolic disorders, particularly T2DM, is the abnormal activation of both the innate and adaptive immune systems, through the recruitment of immune cells in the affected tissues, even in the absence of external pathogens or antigens [69,70]. The direct consequences of these responses and the modulation of immune cell populations depend largely on the metabolic system, altering cellular functionality, increasing the secretion of cytokines and chemokines, as well as the recruitment and activation of leukocyte populations [71]. Therefore, the hyperglycemia in patients with T2DM favors the increase of polymorphonuclear neutrophil leukocytes (PMNs) within the tissues, altering several functions such as cell adhesion, chemotaxis, phagocytosis, and the degradation of antigens, generating tissue damage by these cells. Because periodontitis and T2DM share a complex relationship involving inflammation, hyperinflammation, especially caused by hyperreactive PMNs, plays a crucial role in host tissue destruction in the pathogenesis of periodontitis, since the different phenotypes that present by PMNs act as an important link in both diseases, influencing in their pathogenesis (Figure 1) [72].

Bacteria residing in the gingival sulcus trigger the activation of PMNs, resulting in an increase in the release of molecules with bactericidal properties. These molecules, in turn, are considered responsible for the hallmark characteristics that mark the progression of periodontal disease,

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including the destruction of periodontal [73] tissue and inflammation, which may contribute to metabolic dysregulation [72]. In this context, Herrmann et al. found that patients with periodontitis and T2DM showed a significant increase in gingival PMNs, compared to individuals who only had periodontitis, indicating a hyperinflammatory reaction in the gingival tissue, probably due to T2DM. Therefore, it is suggested that inflammation may be a bilateral factor that can increase the severity and progression of both diseases [74]. The research by Manosudprasit et al. corroborates these findings. In their study, it was observed that the apoptosis of PMNs in the peripheral blood was altered in individuals with T2DM. Furthermore, periodontal disease acted as a confounding factor, meaning that it exerted an additive effect, significantly delaying spontaneous PMNs apoptosis in patients with T2DM and periodontitis. These findings suggest that periodontal disease not only affects the apoptosis of PMNs at the site of periodontal infection, but also has a systemic impact on the resolution of inflammation and clearance of PMNs. This may contribute to the exacerbation of other systemic inflammatory conditions, such as T2DM. In fact, it has been shown that apoptosis of PMNs is delayed in periodontal disease due to the action of TNF-α (Figure 1) [75].

Furthermore, T2DM is considered a significant risk factor for the development of periodontitis [76], because T2DM intensifies the inflammatory response in periodontal tissues, significantly increasing the levels of proinflammatory mediators such as IL-1β and TNF-α, as well as an increase in the activity of matrix metalloproteinases (MMP) [77]. On the other hand, high blood glucose levels attenuate the immune response in patients with T2DM, affecting the recovery of periodontal tissue, which alters the etiopathology of diverse diseases, such as periodontitis [78]. MMPs are enzymes that play a crucial role in tissue remodeling and the breakdown of the extracellular matrix (ECM) [79]. Furthermore, they are involved in the regulation of the activity of various biologically active substrates [80], such as pro- and anti-inflammatory cytokines, chemokines, growth factors, serum components, complement components and cell signaling molecules, which modulate immune responses [81]. MMP-2 is a highly active MMP present in saliva, which plays a crucial role in the degradation of periodontal tissues [82]. Recent studies have established a connection between MMP-2 and periodontitis, since its activity is controlled by tissue inhibitors of matrix metalloproteinases (TIMPs) [83], mainly TIMP-1, a natural inhibitor of MMP-2 produced by periodontal cells, macrophages and monocytes (Figure 1) [84].

During periodontal tissue inflammation, an overexpression of MMP-2 has been observed in saliva and gingival crevicular fluid [85,86]. In the study carried out by Arreguin-Cano et al. (2019), the periodontal status, HbA1c levels, MMP-2 and TIMP-1 activity, and percentage of PMNs in patients with T2DM were compared and analyzed. In this study, an increase in the enzymatic activity of MMP-2 was observed, as well as the expression of TMP-1 according to the severity of periodontitis, this increase being significant in severe periodontitis. In addition, a significant increase in glycosylated hemoglobin (HbA1c) levels was found in patients with moderate and severe periodontitis, suggesting that poor glycemic control is associated with the severity of periodontitis. Likewise, it was observed that in patients with poor glycemic control, there was a significant increase in PMNs, along with a significant decrease in MMP-2 and TMP-1 activity. These findings suggest that in patients with T2DM and poor glycemic control there is an imbalance in MMP-2/TIMP-1, and that the process of inhibition of MMP-2 activity by TIMP-1 is lost in severe periodontitis (Figure 1) [87].

On the other hand, the NLRP3 inflammasome plays an important role during the inflammatory response against infections or cellular stress [88]. In this context, studies have reported a high expression of the NLRP3 inflammasome, both in the gingival tissues of patients with periodontitis [89,90], as well as in cells of the innate immune system and pancreatic β-cells in patients with T2DM [91,92]. In this context, Huang et al. (2015) reported that, both in patients with chronic periodontitis and T2DM, as well as human gingival epithelial cells (HGEC) stimulated with lipopolysaccharide (LPS) and high concentrations of glucose, showed a significant increase in the expression of the NLRP3 inflammasome and IL-1β. These findings suggest that hyperglycemia can exacerbate the inflammatory response of gingival tissue through the NLRP3 pathway, contributing to greater tissue degradation [93], because high levels of IL-1β were significantly associated with periodontitis

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immunopathology, causing periodontal tissue degradation, mainly in alveolar bone absorption and damage to the lamina propria (Figure 1) [94].

3. Periodontitis and Type 2 Diabetes Mellitus

At a clinical level, studies have established an association between periodontitis and adverse outcomes of COVID-19 [95]. Patients with periodontal disease have been shown to be at increased risk of severe COVID-19, including hospitalization, intensive care unit admission, and mortality. Furthermore, periodontal disease may contribute to the severity of COVID-19 by elevating levels of inflammatory biomarkers [96,97]. Conversely, COVID-19 can exacerbate periodontal disease, leading to increased gingival bleeding, dental plaque accumulation, and periodontal pocket deepening (Figure 3) [98,99]. Although there is currently no clear causal relationship, periodontitis represents a risk factor for increasing the severity of COVID-19 [100], by causing microbial dysbiosis, bacterial super-infection, hyperreactivity of the host, and over stimulation of the immune system. Probably due to the set of environmental, microbial and inflammatory factors, which contribute to the progression of the disease [101]. According to Campisi et al. (2021) two interrelated mechanisms may underlie the association between periodontitis and COVID-19. The first mechanism involves a direct viral infection of periodontal tissues, facilitated by the high expression of the ACE2 receptor in these tissues. The second mechanism involves a shared inflammatory response (overexpression of inflammatory cytokines) characterized by a cytokine storm, a condition associated with severe COVID-19 [102] (Figure 2).

Direct contact of the SARS-CoV-2 with periodontal tissues. Periodontitis-induced ulceration of the gingival epithelium may compromise its protective function, increasing the risk of SARS-CoV-2 invasion. Furthermore, the expression of ACE2, transmembrane serine protease (TMPRSS2), and furin, in oral epithelial cells and proteases produced by periodontal-pathogenic bacteria, are necessary to activate the S protein of SARS-CoV-2 and thus bind to host cells and further increase virus infectivity [101,102]. Therefore, it is deduced that aspiration of periodontal-pathogenic bacteria could increase the risk of SARS-CoV-2 infection, since these can increase the expression of ACE2 in the oral cavity, lungs, and bronchi; inducing the production of inflammatory cytokines, such as interleukin IL-6, by alveolar and bronchial epithelial cells, which promotes SARS-CoV-2 infection, and inflammation of the lower respiratory tract can become severe in the presence of pneumonia viral, contributing to the development of cytokine storm and acute respiratory distress syndrome (Figure 2) [95,102].

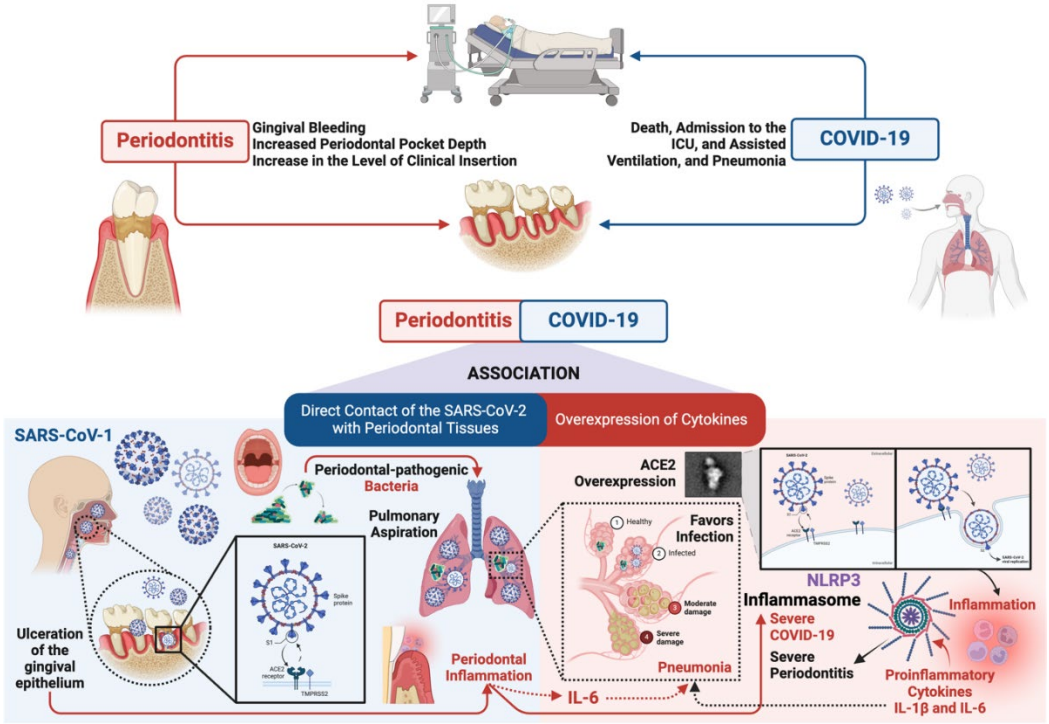

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Figure 2. Relationship between periodontitis and COVID-19. Explanation in the text. Figure created on Biorender.com by Muñoz-Carrillo et al.

Overexpression of cytokines. IL-6, a cytokine overexpressed in periodontitis, has been implicated in the pathogenesis of COVID-19 [103]. SARS-CoV-2 infection induces the release of proinflammatory cytokines, including IL-1β and IL-6, which may contribute to the development of interstitial pneumonia, a hallmark of severe COVID-19. While the causal role of IL-6 in COVID-19 severity remains under investigation, it has been proposed as a potential biomarker for early disease detection and progression monitoring (Figure 2) [102]. In this context, serum IL-6 levels have been correlated with the stage of COVID-19 disease, particularly in patients experiencing respiratory failure. Therefore, elevated IL-6 levels can be used as a predictive biomarker to identify patients at risk for disease progression. Furthermore, increased expression of the IL-6 receptor (IL-6R) and higher levels of IL-6 have been observed in COVID-19 patients who did not survive compared to patients who survived throughout the clinical course of the disease. These findings suggest a potential role of IL-6 in the pathogenesis and progression of COVID-19 [104].

Periodontitis and COVID-19 share several common inflammatory pathways, such as the NLRP3/IL-1β and IL-6 signaling pathway (Figure 2). NF-κB induces the transcriptional expression of NLRP3 and pro-IL-1β [105,106]. Activation of the NLRP3 inflammasome results in the release of pro-inflammatory cytokines IL-1β and IL-18 [107], thereby promoting inflammation and other associated disorders. Inflammatory cytokines can promote the development of low-grade systemic inflammation, leading to the abnormal activation of the NLRP3 inflammasome. This, in turn, can drive chronic inflammatory conditions and influence the pathophysiology of inflammation-related diseases [108]. It has been observed that patients with periodontitis exhibit significantly higher levels of NLRP3, in both blood and saliva. NLRP3 inflammasome-related proteins, such as IL-1β, have been proposed as potential biomarkers for periodontal clinical status [104]. Studies have reported that the expression of these proteins is associated with alveolar bone loss, a hallmark of periodontal disease, and an increase in proinflammatory cytokines, which can contribute to the severity of periodontal disease (Figure 2)[109]. COVID-19 severity has been correlated with NLRP3 inflammasome activation. Post-mortem analysis of COVID-19 patients has revealed persistent NLRP3 inflammasome activation in various tissues and PMNs from peripheral blood [104]. This is because, after viral replication, ACE2 decreases its activity, activating ACE1, leading to elevated levels of PMN, reactive oxygen species, NF-κB, and proinflammatory cytokines, ultimately resulting in inflammatory cell death and tissue damage [110].

4. Type 2 Diabetes Mellitus and COVID-19

Retrospective studies of this group of patients indicate that poor glycemic control is associated with increased morbidity and mortality from COVID-19. However, the severity of COVID-19 is closely correlated with the age of patients, which is often also the case for T2DM [111]. It has been reported that hospitalized patients with COVID-19 and T2DM have almost double the risk of mortality compared to their counterparts without diabetes [112]. In addition, COVID-19 positive patients with T2DM had worse clinical outcomes, exhibiting a severe inflammatory response with a higher risk of admission to the intensive care unit, receiving mechanical ventilation, and in-hospital mortality than those without diabetes (Figure 3) [112,113].

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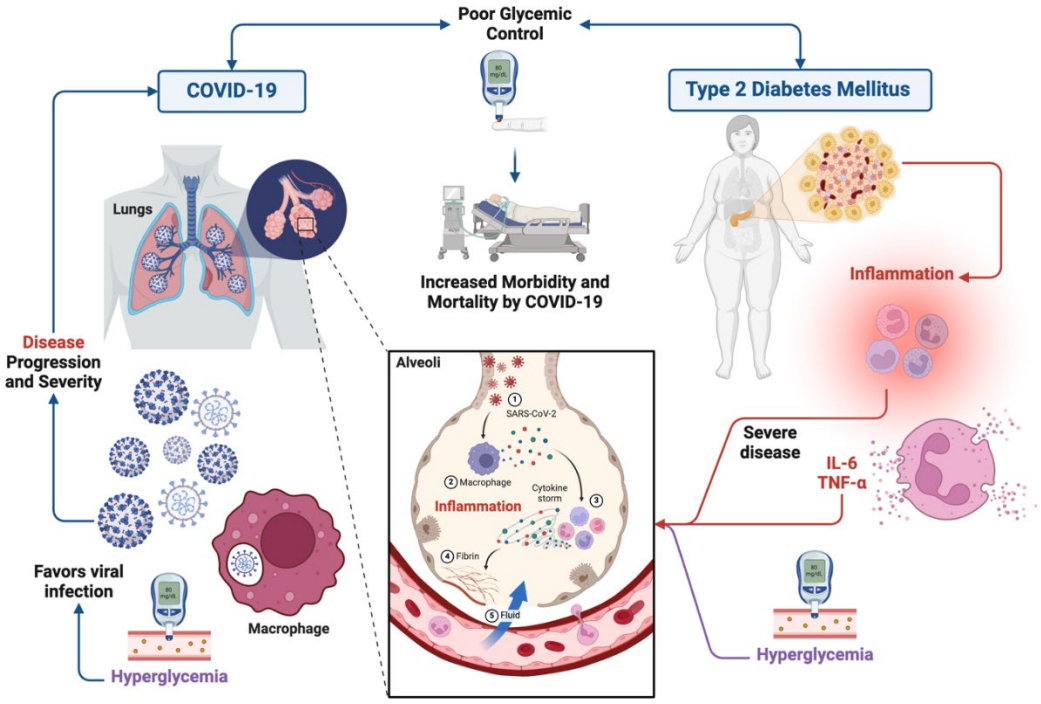

Figure 3. Relationship between type 2 diabetes mellitus and COVID-19. Explanation in the text. Figure created on Biorender.com by Muñoz-Carrillo et al.

The underlying molecular mechanism of how type 2 diabetes mellitus leads to more severe COVID-19 disease is currently unclear [111]. However, this susceptibility of patients with type 2 diabetes mellitus to adverse outcomes associated with SARS-CoV-2 infection is due to impaired immune system function, and possible up regulation of enzymes that mediate viral invasion. Chronic inflammation caused by diabetes, coupled with the acute inflammatory reaction caused by SARS-CoV-2, results in a propensity for inflammatory storm (Figure 3) [114]; which is characterized by the following successive stages: 1) Infection of lung cells by SARS-CoV-2; 2) immune cells, including macrophages, identify the virus and produce cytokines; 3) cytokines attract more immune cells, such as white blood cells, which in turn produce more cytokines, creating a cycle of inflammation that damages lung cells; 4) damage can occur through fibrin formation; and 5) weakened blood vessels allow fluid to leak and fill the lung cavities, causing respiratory failure (Figure 3).

Likewise, it has been reported that patients with type 2 diabetes mellitus and COVID-19 had a higher count of white blood cells, neutrophils, and proinflammatory cytokines (such as IL-6 and TNF-α), suggesting an increased inflammatory response compared to patients without diabetes [112]. In addition to this, the severity of hyperglycemia was associated with the intensity of the cytokine storm, which is a clear indication that immunological triggers are responsible for changes in blood glucose regulation in the context of a severe disease. Furthermore, a fundamental role of alveolar macrophages has been indicated, which increase their glycolytic rate after activation. In this context, SARS-CoV-2 can infect macrophages and benefit from the increase in the glycolytic rate in these cells. Therefore, the presence of a hyperglycemic state in patients with type 2 diabetes mellitus further facilitates viral replication in macrophages, promoting disease progression (Figure 3) [111].

4. Relationship Between Periodontitis, Type 2 Diabetes Mellitus and COVID-19

In the current scientific literature, there is only one systematic review, whose purpose was to carry out a systematic review of the literature, which included 12 studies, to contrast the existing evidence on the relationship between periodontal disease and diabetes mellitus, and the risk of SARS-CoV-2 infection, as well as to establish a hypothesis that explains the ways in which this interaction could occur. Casillas Santana et al. (2021) hypothesize that the relationship between these three

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pathologies is because type 2 diabetes mellitus is a metabolic disorder characterized by hyperglycemia in the blood, the result of altered secretion or action of insulin. Likewise, periodontitis and diabetes mellitus are inflammatory disorders with a bidirectional association, which share a similar immunomodulatory cascade and cytokine profile. On the other hand, ACE2 is a crucial component of the renin-angiotensin system, and a key entry factor into SARS-CoV-2 cells. ACE2 is widely distributed in various tissues including the oral cavity, mainly in the tongue and periodontal tissue. ACE2 expression is modified by chronic uncontrolled glycemia in type 2 diabetes mellitus. Therefore, uncontrolled hyperglycemia increases the risk of developing periodontitis and triggers an overexpression of ACE2 in the periodontal tissue of patients with type 2 diabetes mellitus, these events being potentially essential for SARS-CoV-2 infection and the development of the mild to severe form of COVID-19 [115]. However, this systematic review was carried out in 2021, and has certain limitations, mainly in the search strategy, since the studies evaluated are limited to the English language, excluding studies conducted in Spanish. Therefore, a broader and more exhaustive search is necessary to identify additional literature; and in this way provide a more reliable and precise hypothesis and conclusion on the association of these three pathologies. In this context, this review provides a comprehensive, original and exhaustive perspective on the influence and association of COVID-19 disease with type 2 diabetes mellitus and periodontitis, through three axes, which interrelate these three pathologies.

Currently, there is very little scientific literature on the relationship between periodontitis, type 2 diabetes mellitus and COVID-19 disease. In the present study, we first sought to explain the relationship between the following comorbidities: 1) periodontitis and type 2 diabetes mellitus; 2) periodontitis and COVID-19; and 3) type 2 diabetes mellitus and COVID-19. Based on the systematized reviewed literature, plus the few scientific studies published on the relationship of these three pathologies, we can arrive at the hypothesis, in which the three diseases share three important axes (Figure 4): 1) an axis clinicopathological; 2) an axis associated with glycemia; and 3) an immune axis associated with inflammation.

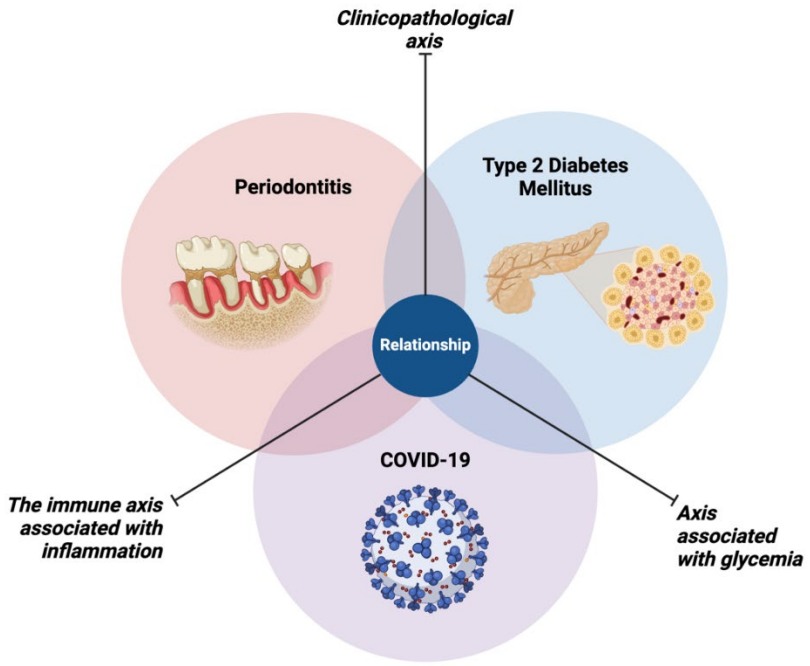

Figure 4. Relationship between periodontitis, type 2 diabetes mellitus and COVID-19. Explanation in the text. Figure created on Biorender.com by Muñoz-Carrillo et al.

Clinicopathological axis. Regarding this axis, studies have reported that patients who suffer from T2DM are more susceptible to developing periodontitis, even in a more severe course of this disease. In turn, patients with poorly controlled T2DM have a higher prevalence of periodontitis with

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a more severe course [15,55–59], evidencing a bidirectional relationship between both pathologies [54]. In turn, poor control of T2DM is associated with high morbidity and mortality by COVID-19, increasing the risk of death, admission to the intensive care unit, and receiving mechanical ventilation [111–113]. Likewise, it has been reported that patients with COVD-19 show a more severe course of periodontitis, and that this, in turn, is associated with complications during COVID-19 disease, including death, admission to the care unit intensive care, need for assisted ventilation and pneumonia [95–99].

Axis associated with glycemia. One of the main characteristics of T2DM is the lack of control of blood glucose, since, if the disease is not controlled, patients who suffer from it, present hyperglycemia. In this context, hyperglycemia triggers many negative effects on the health of patients, including making them more prone to the development of comorbidities with other diseases. On the one hand, hyperglycemia in patients with T2DM favors inflammatory mechanisms that, in turn, can induce insulin resistance [60], decreased endothelial function [68], and an increase in PMN [74]. These factors influence in periodontitis, enhancing the destruction of periodontal tissues, due to the exacerbation of the inflammatory response, generating a more serious course of the disease [87]. Under this context, these conditions favor the infection capacity of SARS-CoV-2 [101]. Furthermore, periodontal-pathogenic bacteria, if aspirated into the lungs, induce the overexpression of ACE2 in the alveoli [101,102], which favors lung inflammation and exacerbated production of proinflammatory cytokines, generating a cytokine storm that induces the destruction of the resident tissue [95,102]. This phenomenon is also closely related to T2DM, since hyperglycemia further enhances the cytokine storm at the lung level, thus increasing the inflammatory response, due to a deterioration of the immune system [114], caused by T2DM, which favors the severity of COVID-19 disease [111].

The immune axis associated with inflammation. The integration of this axis is even more complex, due to the interconnected pathways between periodontitis, T2DM and COVID-19 disease. However, the common denominator within the axis is inflammation. Periodontitis is caused, mainly, by the inflammatory response induced by periodontal-pathogenic bacteria residing in dental plaque [116]. The chronicity of this inflammatory response is characterized by an increase in proinflammatory cytokines, such as TNF-α, IL-1β and IL-6, and immune system cell populations [60]. Particularly, the aberrant production of TNF-α, on the one hand, generates decreased vascular function [68]. On the other hand, it induces the increase and survival of PMN in the periodontal tissue [74,75], which in turn produces MMP-2, which leads to the destruction of periodontal tissue [87]. Likewise, TNF-α modulates the expression of endocan, a proteoglycan that acts as a pro-inflammatory mediator, which is associated with the most severe course of the disease [68]. Regarding IL-1β, this proinflammatory cytokine is associated with the activation of the inflammasome (they are over expression of NLRP3), amplifying the inflammatory response and therefore the destruction of gingival tissue [93]. The intersection between periodontitis, T2DM and COVID-19 disease [95,101], occurs when during diabetes mellitus, there is an increase in blood glucose levels (hyperglycemia) and together with the viral infection, an exacerbated inflammatory response is triggered, increasing the production of TNF-α. IL-1β, IL-6, endocan, NLRP3 inflammasome and an increase in the PMN population, amplifying their effects and leading to a more severe course of comorbidity between these three pathologies [60,68,93,104]. In turn, during COVID-19 disease, periodontitis facilitates the passage of periodontal-pathogenic bacteria, invading the lung, which increase the expression of ACE2, favoring SARS-CoV-2 infection [101,102]; which in turn produces a strong inflammatory response, also characterized by the aberrant production of proinflammatory cytokines (TNF-α, IL-1β and IL-6) [103,104,117], and the activation of alveolar macrophages, which leads to a cytokine storm [114], which ultimately induces tissue destruction at the lung level [102], generating respiratory failure [95,102]. However, this cytokine storm manages to reach the systemic circulation, which reaches the periodontal tissues, also favoring their destruction [110].

5. Conclusion

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Currently, there is very little scientific literature that addresses the relationship between periodontitis, T2DM and the risk of COVID-19 disease. Based on the systematized review of the included studies, we can hypothesize that these three diseases share three important axes that interconnect them: 1) a clinicopathological axis; 2) an axis associated with glycemia; and 3) an immune axis associated with inflammation. Therefore, comorbidity between periodontitis and T2DM represents a greater risk of developing COVID-19 disease with a more severe course.

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