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THE RELATIONSHIP BETWEEN ORAL HEALTH AND CARDIOVASCULAR DISEASE AND DIABETES

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Abstract

Periodontitis is a persistent inflammatory condition caused by the presence of a bacterial biofilm known as dental plaque. It affects the periodontal ligaments and the bone that surrounds the teeth. Over the last several decades, many lines of data have substantiated the correlation between periodontitis and overall health. Periodontitis, a chronic inflammatory condition, has similarities with cardiovascular disease (CVD) and diabetes. Multiple studies have shown a two-way connection between periodontal health and these diseases. Individuals with diabetes have a higher vulnerability to infections and a greater likelihood of developing periodontitis compared to those without this condition. Similarly, it is now clear that periodontitis exacerbates cardiac problems, as shown in both experimental studies and human subjects. Due to these factors, it is very likely that the prevention of periodontitis has an influence on the occurrence or advancement of cardiovascular disease (CVD) and diabetes. In this review, we have presented an updated report on the current understanding of periodontal disease and its negative impact on cardiovascular health and diabetes. We have included information on the latest preclinical research and epidemiological findings.

Keywords: periodontitis, inflammation, bacteria, cardiovascular disease, diabetes.

1. Introduction

Periodontitis is a chronic inflammatory illness caused by several factors. If left untreated, it may cause irreversible damage to the tissues that support the teeth, including the periodontal ligament, cementum, and alveolar bone, ultimately resulting in tooth loss [1]. A crucial factor in the development and advancement of periodontal disease is the presence of a higher concentration of harmful bacteria inside the tooth plaque, which triggers a strong and harmful immune response [2]. An increased concentration of bacterial surface chemicals, namely lipopolysaccharides (LPS), enhances the synthesis of inflammatory mediators and cytokines,

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which in turn increases the release of matrix metalloproteinases (MMPs). Subsequently, these enzymes produced from tissues play a role in the process of modifying the extracellular matrix and causing bone deterioration [3,4]. Significantly, new research has definitively shown that these harmful impacts are not just limited to the mouth but may impact a person's general well-being. Due to this specific rationale, research on the systemic impact of periodontitis has increased significantly [5].

Periodontal bacteria have the ability to damage the epithelium of the periodontal pocket, which then permits harmful endotoxins and exotoxins to enter the circulation [2]. This process results in the spread of germs throughout the body, leading to a systemic infection and an increase in the body's inflammatory response. Periodontal pathogens have been found in several tissues and organs of the cardiovascular system, including as human cardiac tissue, pericardial fluids, heart valves, and atherosclerotic lesions [6,7,8,9,10,11,12,13]. In recent decades, periodontitis has been linked to the development of systemic illnesses like as cardiovascular disease (CVDs) and diabetes [14,15,16].

Two meta-analyses, conducted by Janket et al. and Kofhader and colleagues, have examined the possible connection between oral disease and cardiovascular disease (CVD). They have concluded that periodontal disease could be a risk factor for cardiovascular events, including stroke and coronary heart disease [17,18]. Moreover, prior studies have shown that persons with periodontitis have a much higher likelihood of acquiring cardiovascular diseases (CVDs), such as myocardial infarction, heart failure, peripheral artery disease (PAD), atherosclerosis, and stroke [16,19].

Curiously, researchers have also investigated the connection between periodontitis and diabetes. Multiple investigations indicate that this correlation is reciprocal [20]. Individuals with diabetes have a higher likelihood of developing periodontitis. Additionally, those who have both periodontitis and diabetes have worse glycemic control [21,22]. Hence, it is crucial to educate healthcare workers on the implications of oral disorders, since they might possibly be linked to many pathological problems. The purpose of this study was to provide an updated overview to physicians and fundamental scientists of the existing data, both experimental and clinical, that supports the correlation between periodontal disease and cardiovascular diseases (CVDs).

2. The pathogenesis of periodontitis

An imbalance of microorganisms in dental plaque, known as dysbiosis, is a significant cause of persistent gingivitis and periodontitis [2,23]. Furthermore, periodontitis is linked to, and likely triggered by, a modified and complex interplay between particular subgingival microorganisms, immunological responses of the host, harmful environmental exposure, and hereditary factors [24]. Currently, about 800 distinct kinds of bacteria have been found and thoroughly described in human dental plaque.

The potential pathogens that are of importance in this context include both Gram-negative and Gram-positive organisms. These include *Aggregatibacter actinomycetemcomitans*, *Treponema denticola*, *Prevotella intermedia*, *Parvimonas micra*, *Campylobacter rectus*, *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Eubacterium timidum* [25,26]. In terms of the underlying mechanisms, infections often result in the development of gingival lesions, along with the spread of bacteria to the tissues around the teeth [2,23]. Subsequently, the lesion advances to periodontitis when bacterial infection and the resulting inflammatory response invade the root surface and penetrate the supporting tissues of the teeth [2,23] (Figure 1).

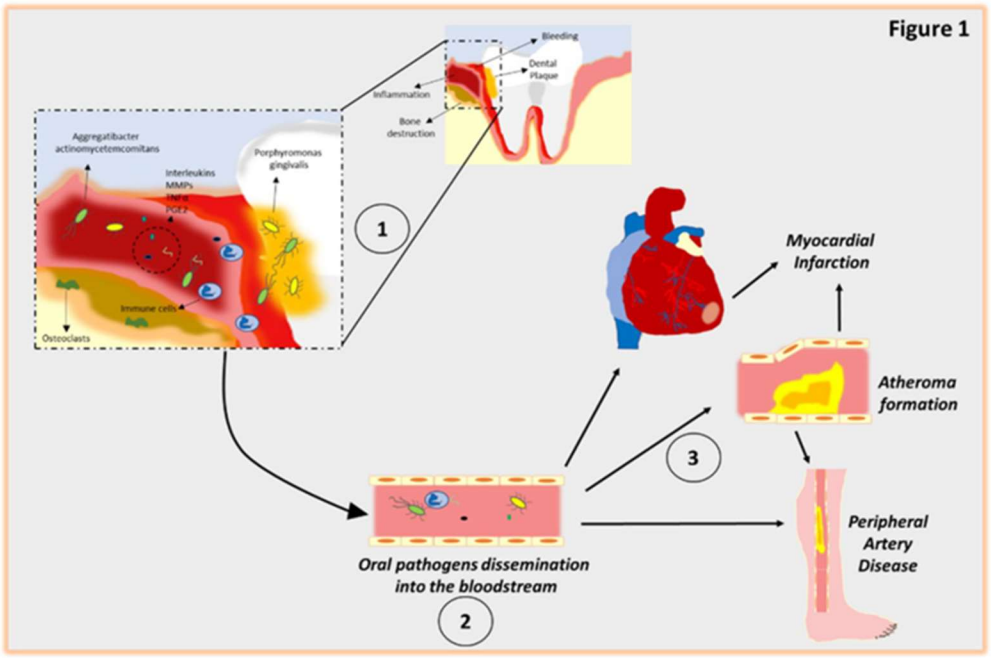

Figure 1. A diagrammatic illustration of the inflammatory pathways that connect periodontitis to cardiovascular diseases (CVDs).

Typically, the process of inflammation starts with the migration of phagocytes (neutrophils and macrophages) to the site of injury. Significantly, the gingival epithelium plays a role in promoting this process by releasing chemical mediators such as interleukins (ILs), prostaglandin E2 (PGE2), and tumor necrosis factor alpha (TNF-α), which attract neutrophils [27,28]. In addition, these phagocytic cells possess specialized receptors, known as Toll-like receptors (TLRs), on their plasma membrane. These receptors are responsible for recognizing and binding to surface molecules of bacteria [27,28]. Similarly, the plasma proteins of the complement system interact with each other to enhance the vulnerability of pathogens to the phagocytic cells' activity [28].

The primary purpose of this first reaction is to eradicate and remove microorganisms, and then effectively eliminate the ensuing cellular waste (necrotic tissue and apoptotic neutrophils) by the action of mononuclear cells, such as monocytes and macrophages [28]. It is important to emphasize that a strong and well-functioning immune system does not cause any harm to the

tissue around the tooth, and it effectively eliminates the bacterial infection [29,30]. However, if bacteria species persist in growing or if there is a faulty or modified immune response, the initial periodontal inflammation becomes chronic, leading to the production of additional mediators [28,30]. These processes lead to the recruitment of other kinds of immune cells, such as T-cells and monocytes. Subsequently, the extended inflammatory process triggers the removal of alveolar bone by osteoclasts and the breakdown of ligament fibers by MMPs, while also leading to the development of granulation tissue [31]. Furthermore, as previously mentioned, this ongoing long-term inflammatory process may result in harmful consequences that may establish a connection between periodontal disease and other conditions such as diabetes and cardiovascular disease (Figure 1).

3. The Relationship Between Diabetes and Periodontal Disease

Diabetes mellitus (DM) is a medical condition marked by high levels of sugar in the blood, resulting from a lack of insulin production and/or the body's inability to effectively utilize insulin. This insufficiency may be either hereditary or acquired. [32,33] Significantly, a connection between DM (diabetes mellitus) and periodontitis has been shown in the literature since the 1960s. Subsequent findings have unequivocally shown a connection between diabetes mellitus (DM) and periodontal disease in both animals and people [33].

Blasco-baque and associates conducted animal investigations that showed evidence for the involvement of periodontal dysbiosis in the onset of insulin resistance [34]. In addition, Liu and colleagues showed that periodontal disease worsened the decline of pancreatic β-cell function and increased insulin resistance in diabetic mice [35]. Crucially, research in people has shown that treating periodontal disease may lower glycated hemoglobin levels in diabetes individuals [36,37,38,39]. In addition, a recent observational research conducted on persons aged 40 years or older found that periodontitis was more common in those with diabetes compared to those without diabetes. This effect was seen regardless of gender and age [40]. The precise mechanism between DM and periodontal disease has not yet been completely understood. It is worth mentioning that several research have shown that DM has a role in changing the bacterial population in the area below the gum line by modifying the substances present, creating a favorable environment for the development of harmful bacteria [41,42,43,44,45].

Moreover, higher levels of inflammatory mediators such as C-reactive protein (CRP), TNF-α, and IL-6 in periodontal disorders may serve as the crucial link between DM and periodontitis [27,45,46,47,48,49]. In 2010, Chen Lei and colleagues presented data indicating a correlation between periodontitis and higher levels of glycated hemoglobin (HbA1c) and CRP in individuals with diabetes mellitus [49]. Furthermore, in 2012, the authors of the study proposed that periodontal care was linked to a decrease in CRP levels in individuals with diabetes mellitus [50]. Consistent with these studies, Quintero and colleagues have shown that periodontal treatment may also decrease HbA1c levels in individuals with DM. The user's text is "[51]."

A recent meta-analysis conducted by Grellmann and colleagues provided results that strongly supports the use of systemic antibiotics for individuals with diabetes and periodontitis, demonstrating an extra beneficial benefit [52]. On the other hand, a comprehensive analysis conducted by Lira Junior and his team revealed that the supplementary use of systemic antibiotics did not provide any extra advantages in terms of lowering HbA1c levels in diabetic patients [53].

Oxidative stress is a significant connection between DM and periodontitis, since it may trigger pro-inflammatory pathways that are shared by both conditions [54]. Allen and colleagues have shown that individuals with periodontitis who also have DM have elevated levels of plasma indicators of oxidative stress, which may trigger systemic pro-inflammatory pathways [55]. Nevertheless, it is crucial to emphasize that several research have not shown a correlation between diabetes and periodontal disease [56]. Additional researches are necessary to verify the probable connection between these two widely frequent illnesses.

4. A mechanistic model explaining the connection between periodontal disease and cardiovascular disease

While there is evidence of a possible correlation between cardiovascular disease (CVD) and periodontitis in clinical settings, the specific mechanism linking these two conditions has not yet been fully understood. However, the primary mechanism that explains this association is the spread of oral pathogens into the circulation (Figure 1). For example, bacteremia, which is often produced by both non-surgical and surgical dental treatments, is a significant cause of infective endocarditis in those who are prone to heart disease. Therefore, individuals with heart illness who are having dental treatments are offered prophylaxis [57].

It is worth mentioning that periodontal infections have the ability to directly infiltrate many organs and tissues, including as the circulatory system. Louhelainen and his colleagues have recently shown that in patients with pericarditis, over half (~60%) of the pericardial fluids tested positive for bacteria associated to endodontitis, while the remaining group (~40% of patients) tested positive for periodontal pathogens [6]. Similarly, Oliveira and colleagues discovered that periodontal bacteria were found in the heart valve tissue of individuals with valve disease [58]. In addition, Ziebold and colleagues provided evidence of the existence of oral bacteria DNA in both atrial and ventricular tissues of individuals who had aortic valve surgery [13].

In pre-clinical studies, Sekinishi and colleagues showed that injecting *Aggregatibacter actinomycetemcomitans*, a periodontal pathogen, into mice undergoing transverse aortic constriction (TAC) caused a notable decline in cardiac function compared to the control group (TAC mice injected with PBS). This phenomenon was associated by an increased cardiac fibrosis and hypertrophy, as well as an intensified atherosclerosis [59]. Remarkably, the infection caused by *Aggregatibacter actinomycetemcomitans* led to a significant elevation in the expression of MMP-2 in the interstitial tissue [59]. MMPs, or matrix metalloproteinases, are crucial proteins that are triggered by periodontal pathogens. They play a role in both normal

tissue remodeling and the abnormal breakdown of the extracellular matrix (ECM). These processes are important in the development of periodontitis, a disease of the gums and supporting structures of the teeth [31].

5. Summary

This study examines the possible correlation between periodontal disease and cardiovascular diseases (CVDs). Furthermore, we elucidated the correlation between periodontitis and diabetes. Therefore, the objective of this research was to enhance the knowledge and consciousness of both physicians and scientists about the need for a more comprehensive comprehension of how the prevention of periodontal disease might influence cardiovascular disease (CVD) and diabetes. Implementing these steps would not only provide extra preventive strategies for cardiovascular diseases, but also reduce the financial strain on the healthcare system. Therefore, it is crucial for good health policy to prioritize periodontitis as a risk factor connected to cardiovascular disease (CVD), given the significance of avoiding and treating all long-lasting infections.

Therefore, along with diet, exercise, and smoking cessation, it is essential to include preventive periodontal therapies as a crucial component of any adult health program aimed at avoiding or better managing cardiovascular disease (CVD).

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