WHY PATIENTS WITH CARDIOVASCULAR RISK SHOULD GO TO DENTIST: IS THERE SUFFICIENT EVIDENCE OF INFLUENCE OF PERIODONTAL THERAPY ON CARDIOVASCULAR DISEASE?

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Cardiovascular disease (CVD) is a common cause of death, representing 29% of the mortality all over the word. More than 70 million Americans have been diagnosed with various forms of CVD, including high blood pressure, coronary artery disease (acute myocardial infarction and angina pectoris), disorders of peripheral arteries. There is strong evidence that periodontal disease (PD) is associated with an increased risk of CVD. In addition, many patients with CVD are also affected by PD, which can be mild or severe. The aim of this manuscript is to investigate the effects of periodontal therapy on the management of CVD. Thirty-four randomised controlled trials and reviews were included in this manuscript to test the effects of different periodontal therapies for patients with CVD. In conclusion, we may affirm that there is some lack of knowledge on the relationship between PD and CVD, however there is sufficient evidence to justify a periodontal treatment to prevent CVD; in fact, PD is very prevalent in the middle-aged population and can have a significant impact on the cardiovascular function.

For decades doctors and dentists have turned their attention to their respective fields of action. However, recent studies have strongly suggested that oral health may be indicative of systemic health. Currently, this gap between medicine and dentistry is rapidly shrinking, because there are substantial data supporting the idea of a close association between periodontal disease (PD) and systemic conditions, such as cardiovascular disease, diabetes, adverse reactions in pregnancy, osteoporosis, oral lesions (1-10). Therefore, there is reason to hope that the strong evidence identified to date by these studies could lead to significant improvements in treatment of periodontal infections (6, 11-20) and may bring about an improvement of systemic conditions also. For this reason, researchers must continue not only to discover more information on the correlation between PD and systemic diseases, but also focus their attention on the positive associations that may arise from the treatment of the oral cavity as a way to increase the healing of systemic diseases.

The term periodontal disease (PD) is generally used to describe diseases affecting the gums and tooth support tissues, causing damage to the connective tissue and alveolar bone (21). PD is caused by specific bacteria of the biofilm formed by plaque. The bacteria leak into the periodontal ligament space, causing anaerobic infection and creating a cascade of events which end with the production of inflammatory mediators and bacterial metabolites (22). At least two potential metabolic pathways could develop from the periodontal pocket and as a result

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of this condition could lead to a localized infectious-inflammatory disease involving other organs. The first step is the passage of periodontal pathogens and their products through the ulcerated epithelium into the bloodstream, leading to bacteremia and/or causing a systemic immune response. The second step is the passage of inflammatory mediators from the periodontal pocket into the bloodstream (22).

The pathological mechanisms by which PD may contribute to the pathogenesis of systemic inflammatory diseases are currently the topic of intensive research. Thousands of different kinds of bacteria and various viruses are associated to the composition of the plaque and are involved in the etiopathogenesis of PD. The most frequently identified include three species called "red complex": *Porphyromonas gingivalis, Tannerella forsythia, and Treponema denticola* (23).

Periodontal disease and cardiovascular disease

Cardiovascular disease (CVD) is a common cause of death, representing 29% of the mortality all over the word. More than 70 million Americans have been diagnosed with various forms of CVD, including high blood pressure, coronary artery disease (acute myocardial infarction and angina pectoris), disorders of peripheral arteries etc. The main cause of these CVDs is atherosclerosis, which is responsible for 50% of deaths in the United States, Europe and Japan (24).

After eliminating other risk factors, some studies indicate that severe PD is associated with an increased risk of CVD ranging from 25% to 90%; 8.91% of patients with CVD are also affected by PD, which can be mild or severe. While 66% of subjects with CVD also suffer from PD (25). These data must be explained also by the fact that CVD and PD share similar risk factors such as smoking, diabetes mellitus, obesity and hypertension (26). In literature some studies demonstrated a mild-moderate association between CVD and PD (27-29).

In one study, Ziegler et al. (30) demonstrated that the depth of pathological periodontal pockets is related to diastolic blood pressure in obese adolescents. This association was unaffected by other risk markers for cardiovascular events or periodontal disease. In addition, Kumar reported that a persistent infection, such as chronic periodontitis, may influence changes in the systemic levels of high-sensitivity C-reactive protein (HsCRP), LDL and HDL, which potentially have an impact on inflammation-associated atherosclerotic processes, such as CVD (31). Another study affirmed that PD was a significant risk factor in people aged over 40 years, who had coronary artery disease proved by coronary angiography (32). Another clinical trial provided new evidence regarding the positive effect of periodontal treatment on risk markers for recurrence of cardiovascular events in stable coronary artery disease patients (33). A recent randomized controlled trial concluded that the use of Triclosan-toothpaste had influence on biomarkers of cardiovascular risk. However, it is unclear whether this influence is clinically significant. The reason why PD therapy could modify CVD management is still unknown (34).

On the contrary, a recent study found insufficient evidence to support or refute whether periodontal therapy can prevent the recurrence of CVD in the long term in patients with chronic periodontitis. No evidence on primary prevention was found (35). Likewise, in the study previously cited, Thomopoulos stated that from the clinical point of view, advising periodontal prevention or treatment targeting on the prevention of CVD is unjustified. By contrast, oral hygiene including periodontal health might contribute to an overall well-being and healthy lifestyle and therefore may, at least partially, contribute to cardiovascular prevention (36).

Hypothesis on mechanism of action

The presence of pathogenic bacteria correlated with periodontal disease may be localized in plasma or ateromasic plaques (37, 38). Investigating these plaques, Cairo et al. identified various bacteria: *T. forsynthensis* (79%), *F. nucleatum* (63%), *P. intermedia* (53%), *P. gingivalis* (37%) and *A. actinomycetemcomitans* (5%) (39). These bacteria can also be found in the carotid, coronary and occluded arteries of patients who have Buerger disease (40). The pathogens induce the release of inflammatory cytokines; even normal chewing

contributes to the spread of pro-inflammatory cytokines from the mouth into the bloodstream (TNF, IL-1 and PGE2) (41). Animal studies have been able to demonstrate atherosclerosis induced by pathogenic bacteria of PD (42).

The presence of acute or chronic infections may play a significant role on CVD onset, causing increased vascular inflammation and thrombosis promotion (43, 44). These infections may be considered a secondary pathogenic pathway (45, 46), among which PD might be the most common.

There are two main hypothesised ways for pathogenesis: i) direct invasion by the bacteria into the endothelial vascular wall; and ii) release, in response to infection, of inflammatory mediators with atherogenic systemic effects. These micro-organisms, in particular the species *P. gingivalis*, have demonstrated the ability to interact with the surface of endothelial cells and induce smooth cell proliferation (47, 48). In addition, platelets could be activated and aggregated by periodontal pathogens present in the atheromas through collagen-like platelet aggregation-associated protein expression. The activated and aggregated platelets could induce atheroma formation and thrombosis, finally leading to CVD (49).

In patients with CVD, the serological inflammatory markers are significantly higher, suggesting that CVD may contribute to inflammation of the soft tissues, causing gingivitis, periodontitis or pericoronitis. A high proportion of patients with hypertension develop PD, and many antihypertensive medications may cause xerostomia that increase oral mucosa inflammation (50). As previously cited, the reason why PD therapy could modify CVD management is still unknown, but a recent study reports that microparticles could be the missing link between PD therapy and improvement in PD management. In fact, the rational of considering periodontitis as risk factor for systemic disease is the passage of inflammatory cytokines and/or bacteria into the bloodstream, thus causing systemic disease in distant organs. Membrane microparticles are released by multiple cells in inflammatory environments. Recent data suggested the role of these microparticles in the pathogenic process of many systemic diseases that can be also associated to periodontitis. Periodontitis could therefore be a chronic reservoir of microparticles, hence partially elucidating the interaction with systemic disease initiation or progression (51).

Other studies confirm that periodontal therapy improves serological markers of CVD. In fact, when PD is active, the levels of systemic inflammation markers are increased and, when PD is treated, the level of systemic inflammatory mediators significantly decrease (52, 53). Oral health and a pleasant smile are a goal of every person and a civil society. Therefore all dental disciplines must contribute to this goal and all dentists must guarantee their patients the best possible care (54-61).

CONCLUSIONS

There is some lack of knowledge on the relationship between PD and CVD. There is sufficient evidence to justify periodontal treatment to prevent CVD. There are factors that can affect both diseases as genetic factors (IL-6, IL-10, Vitamin D-receptor), environmental factors (smoking, diabetes, stress etc.), and impaired immune response. However, PD is highly prevalent in the middle-aged population and can have a significant impact on cardiovascular function.

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