



Review

# Periodontal Disease: A Risk Factor for Diabetes and Cardiovascular Disease

Daniela Liccardo <sup>1</sup>, Alessandro Cannavo <sup>1,2,\*</sup>, Gianrico Spagnuolo <sup>3,4</sup> , Nicola Ferrara <sup>1,5</sup> , Antonio Cittadini <sup>1</sup>, Carlo Rengo <sup>6</sup> and Giuseppe Rengo <sup>1,5</sup>

<sup>1</sup> Department of Translational Medical Sciences, Federico II University of Naples, 80131 Naples, Italy; liccardo.daniela@gmail.com (D.L.); nicola.ferrara@unina.it (N.F.); antonio.cittadini@unina.it (A.C.); giuseppe.rengo@unina.it (G.R.)

<sup>2</sup> Center for Translational Medicine, Temple University, Philadelphia, PA 19140, USA

<sup>3</sup> Department of Neurosciences, Reproductive and Odontostomatological Sciences, Federico II University of Naples, 80131 Naples, Italy; gianrico.spagnuolo@gmail.com

<sup>4</sup> Institute of Dentistry, I.M. Sechenov First Moscow State Medical University, 119146 Moscow, Russia

<sup>5</sup> Istituti Clinici Scientifici-ICS Maugeri S.p.A., 82037 Telese Terme (BN), Italy

<sup>6</sup> Department of Prosthodontics and Dental Materials, School of Dental Medicine, University of Siena, 53100 Siena, Italy; carlorenzo@alice.it

\* Correspondence: alessandro.cannavo@unina.it; Tel.: +39-0817-463-677

Received: 9 February 2019; Accepted: 18 March 2019; Published: 20 March 2019



**Abstract:** Periodontitis is a chronic inflammatory disease, initiated by the presence of a bacterial biofilm, called dental plaque, which affects both the periodontal ligaments and bone surrounding teeth. In the last decades, several lines of evidence have supported the existence of a relationship between periodontitis and systemic health. For instance, as periodontitis acts within the same chronic inflammatory model seen in cardiovascular disease (CVD), or other disorders, such as diabetes, several studies have suggested the existence of a bi-directional link between periodontal health and these pathologies. For instance, people with diabetes are more susceptible to infections and are more likely to suffer from periodontitis than people without this syndrome. Analogously, it is now evident that cardiac disorders are worsened by periodontitis, both experimentally and in humans. For all these reasons, it is very plausible that preventing periodontitis has an impact on the onset or progression of CVD and diabetes. On these grounds, in this review, we have provided an updated account on the current knowledge concerning periodontal disease and the adverse effects exerted on the cardiovascular system health and diabetes, informing readers on the most recent preclinical studies and epidemiological evidence.

**Keywords:** periodontitis; inflammation; bacteria; cardiovascular disease; diabetes

## 1. Introduction

Periodontitis is a multifactorial, chronic inflammatory disorder, that can lead, if untreated, to the non-reversible damage of supportive tissues (periodontal ligament, cementum and alveolar bone) surrounding the teeth with consequent tooth loss [1]. Importantly, one of the major determinants of the development and progression of periodontal disease is represented by an increased concentration of pathogenic bacteria, within the dental plaque, that activates a massive noxious immune response [2]. For instance, the augmented concentration of bacterial surface molecules, such as lipopolysaccharides (LPS), stimulates the production of inflammatory mediators and cytokines that, in turn, promotes the release of the matrix metalloproteinases (MMPs). These tissue-derived enzymes then participate in the extracellular matrix remodelling and bone destruction [3,4]. Importantly, recent studies have clearly proven that these deleterious effects are not only restricted to the oral cavity but can affect the

overall health of an individual. For this very reason, research involving the systemic implication of periodontitis has grown exponentially [5]. Indeed, periodontal pathogens can destroy the epithelium of the periodontal pocket thus allowing the entry of noxious endotoxins and exotoxins into the bloodstream [2]. This process leads to bacterial dissemination and systemic infection, with a consequent rise in inflammatory response. For instance, periodontal pathogens have been detected in disparate tissues and organs of the cardiovascular system including human cardiac tissue, pericardial fluids, heart valves and in atherosclerotic lesions [6–13]. For these reasons, in the last decades, periodontitis has been associated with the onset of systemic disorders including cardiovascular disease (CVDs) and diabetes [14–16]. In this regard, two meta-analyses, by Janket et al. and Kofhader and colleagues respectively, have evaluated the potential correlation between oral disease and CVD, concluding that periodontal disease is a potential risk factor for cardiovascular (CV) events, such as stroke and coronary heart disease [17,18]. Furthermore, it has been previously demonstrated that individuals with periodontitis have a sensible increased risk of developing CVDs, including myocardial infarction, heart failure, peripheral artery disease (PAD), atherosclerosis and stroke [16,19].

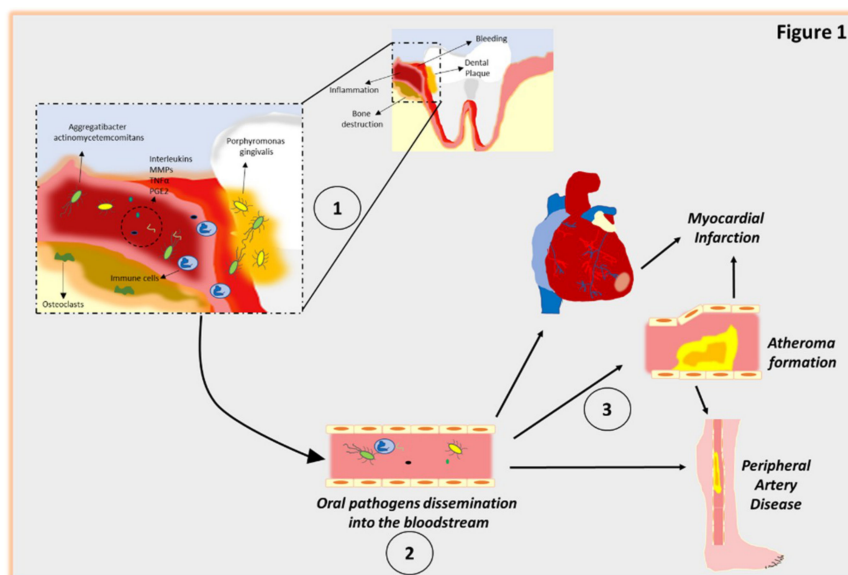
Interestingly, the link between periodontitis and diabetes has also been pursued. Several studies suggest that this association is bi-directional [20]. Indeed, individuals with diabetes are more likely to develop periodontitis and those subjects with periodontitis, and diabetes, present a worse glycemic control [21,22]. Therefore, based on this premise, it is of paramount importance to inform health professionals about the consequence of diseases affecting the oral cavity in that these are potentially associated with a range of pathologic conditions. Thus, the aim of this review was to update clinicians and basic scientists about the current evidence (experimental and clinical) that supports the existence of the relationship between periodontal disease and CVDs.

## 2. Pathogenesis of Periodontitis

An imbalance of micro-organisms forming the dental plaque (dysbiosis) is a major triggering factor for chronic gingivitis and periodontitis [2,23]. In addition, periodontitis is associated with, and probably caused by, an altered dynamic interaction among specific subgingival microbes, host immune responses, hazardous environmental exposure and genetic factors [24]. To date, almost 800 different species of bacteria have been identified and characterized in human dental plaque. Of relevance, the putative pathogens include Gram-negative and -positive members, such as *Treponema denticola*, *Tannerella forsythia*, *Prevotella intermedia*, *Agregatibacter actinomycetemcomitans*, *Campylobacter rectus*, *Eubacterium timidum*, *Parvimonas micra* and *Porphyromonas gingivalis* [25, 26]. Mechanistically, infections usually lead to gingival lesions with contamination of tissues surrounding the teeth [2,23]. Then, the lesion progresses to periodontitis once bacterial infection, and the subsequent inflammatory response, tackles the root surface, penetrating the supporting structures of the teeth [2,23] (Figure 1).

In general, the inflammation process begins with phagocytes (neutrophils and macrophages) that migrate to the lesion site. Importantly, this process is, at least in part, promoted by the gingival epithelium that releases chemical mediators including interleukins (ILs), prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF- $\alpha$ ), that recruit neutrophils [27,28]. Furthermore, these phagocytic cells express on their plasma membrane specific receptors that recognize and bind surface molecules of bacteria (i.e., Toll-like receptors, TLRs) [27,28]. Analogously, the plasma proteins of the complement system react with one another to make pathogens more susceptible to the action of these phagocytic cells [28]. The function of this initial response includes the killing and elimination of microbes followed by an efficient clearance of the resulting cellular debris (necrotic tissue and apoptotic neutrophils) by mononuclear cells, such as monocytes and macrophages [28]. It is worth stressing that in an effective and healthy immune system, there is no damage to the tissue surrounding the tooth and the bacterial insult is efficiently removed [29,30]. However, when microbial species continue to grow, or if there is a defective/altered immune response, the acute periodontal inflammation becomes chronic and additional mediators are produced [28,30]. These events result in the recruitment of more immuno-cell

types, such as T-cells and monocytes. Then, this prolonged inflammatory process induces alveolar bone reabsorption, by osteoclasts, and degradation of ligament fibers by MMPs, as well as the formation of the granulation tissue [31]. Moreover, as discussed above, this sustained chronic inflammatory process can lead to noxious effects that could link periodontal disease to other disorders including diabetes and CVD (Figure 1).



**Figure 1.** Schematic representation of inflammatory mechanisms linking periodontitis to CVDs. (1) The imbalance in pathogens of the biofilm leads to gingival epithelium inflammation that releases chemical mediators, such as interleukins (ILs), prostaglandin E2 (PGE2), tumor necrosis factor alpha (TNF- $\alpha$ ) and MMPs, that recruit immune cells. This inflammatory response induces alveolar bone reabsorption, by osteoclasts. (2) At a chronic stage, oral pathogenic dissemination into the bloodstream leads to the onset of CVDs including atherosclerosis, myocardial infarction and peripheral artery disease (3).

### 3. Diabetes and Periodontal Disease

Diabetes mellitus (DM) is a clinical syndrome, characterized by hyperglycemia, caused by inherited and/or acquired deficiency in insulin production and/or action [32,33]. Importantly, an association between DM and periodontitis was reported in the literature dating back to the 1960s. Since then, several reports have clearly demonstrated an association between DM and periodontal disease in both animals and humans [33]. For instance, in animal studies, Blasco-baque and coworkers recently provided data supporting the role of periodontal dysbiosis in the development of insulin resistance [34]. Moreover, Liu and coworkers demonstrated that periodontal disease aggravated pancreatic  $\beta$ -cell failure and insulin resistance in diabetic mice [35]. Importantly, evidence in humans has demonstrated that treating periodontal disease is able to reduce glycated hemoglobin in diabetic patients [36–39]. Furthermore, a recent observational study, performed in subjects aged 40 years or over, demonstrated that periodontitis was significantly more prevalent among individuals suffering from diabetes than non-diabetic ones, with no difference in terms of gender and age [40]. The specific mechanism connecting DM and periodontal disease has not been fully elucidated yet. Of note, several reports have suggested that DM participates in altering the subgingival bacterial community through substrate-related alterations offering a microenvironment favorable for the pathogens growth [41–45]. Furthermore, systemic levels of inflammatory mediators, including C-reactive protein (CRP), TNF- $\alpha$ , and IL-6, which are elevated in periodontal diseases, may represent the linchpin between DM and periodontitis [27,45–49]. For instance, in 2010 Chen Lei and coworkers provided data showing that periodontitis correlated with increased levels of glycated hemoglobin (HbA1c) and CRP observed in DM patients [49]. Moreover, in 2012 the same authors suggested that periodontal therapy was

associated with CRP levels reduction in DM subjects [50]. In line with these reports, Quintero and colleagues have demonstrated that, periodontal therapy can also reduce HbA1c levels in subjects with DM [51]. Most importantly, data from a recent meta-analysis, by Grellmann and coworkers, supported the additional effect of the use of systemic antibiotics for subjects with diabetes and periodontitis [52]. However, in contrast with these data, a systematic review from Lira Junior and colleagues demonstrated that adjunctive use of systemic antibiotics did not provide any additional benefit in terms of the reduction of HbA1c in diabetic patients [53].

Finally, oxidative stress appears to be another major link between DM and periodontitis, since it can activate pro-inflammatory pathways common to these pathologies [54]. In this regard, Allen and colleagues have observed that DM, in patients with periodontitis, is associated with higher levels of plasma biomarkers of oxidative stress that may activate systemic pro-inflammatory pathways [55]. However, it is important to underline that several reports failed to show an association between diabetes and periodontal disease [56]. For this main reason, further investigations are warranted to confirm the potential link between these two highly prevalent disorders.

#### 4. Periodontitis as a Risk Factor of Cardiovascular Disease

In the last two decades, several studies have showed that individuals with periodontitis are at higher risk of CV events, including, myocardial infarction, peripheral artery disease, stroke and heart failure (HF).

##### 4.1. Myocardial Infarction

Myocardial infarction and periodontal disease share several common risk factors, including diabetes, smoking and inflammation [57–59]. For this reason, a growing body of evidence suggests that periodontal disease is associated with increased myocardial infarction risk [60–63]. Of note, in the 1980s Mattila and colleagues observed that dental health was significantly worse in patients with myocardial infarction than healthy controls [64]. Twenty-years later, Willershausen and coworkers demonstrated that there was a strict association between chronic dental infection and acute myocardial infarction [65]. Further to this, Jansson and coworkers suggested that oral disease could be used as a risk indicator of death due to CVD, especially when this was combined with other well-established risk factors, such as smoking [66].

Importantly, pre-clinical studies have also supported such a relationship. For instance, Akamatsu and colleagues demonstrated that, in mice, periodontal pathogens induced myocarditis and/or myocardial infarction [67].

However, since both myocardial infarction and periodontal disease are multifactorial in nature, some issues have been raised concerning the legitimacy of evidence sustaining such an association. Indeed, several epidemiologic studies failed to observe such a relationship [68,69]. Recently, one systematic review by Sidhu and coworkers concluded that no relationship between periodontal disease and myocardial infarction could have been exactly replicated or confirmed [70]. Therefore, since not enough evidence is available so far, the possibility that periodontal treatments are able to prevent the onset of myocardial infarction or the progression of post-myocardial infarction cardiac disease remains inadequately supported by factual evidence. Of note, this conclusion was congruent with a recent report from the American Heart Association [71]. Despite this, through the years, several studies continue to accumulate data regarding the presence of a specific relationship between periodontal disease and CVDs, including myocardial infarction, and potential mechanistic models have been proposed (discussed in the next paragraph) [72].

##### 4.2. Endothelial Dysfunction

Endothelial dysfunction is an independent predictor of cardiovascular events and precedes the development of atherosclerosis and other CVDs [73]. This pathological process is usually caused by the reduced bioavailability of endogenous molecules, such as nitric oxide (NO<sup>•</sup>), a gasotransmitter that

constrains platelet aggregation, inhibits the attachment of leukocytes to endothelial cells and prevents the expression of adhesion molecules [73,74]. Several lines of evidence have suggested a link between periodontitis and endothelial dysfunction. For instance, in 2008, Higashi and colleagues demonstrated that, in human subjects affected by periodontitis, endothelial dysfunction without cardiovascular risk factors or with hypertension, was due to a marked reduction in NO bioavailability and to systemic inflammation [75]. In line with this report, Moura and coworkers recently demonstrated a potential correlation between salivary NO concentration and endothelial dysfunction in patients with periodontal disease [76]. Furthermore, studies in experimental models of periodontitis in rats, have confirmed that reduced NO levels correlated with the onset of endothelial dysfunction [77,78]. Of note, a number of reports have also suggested that endotoxins and antigens secreted by periodontal bacteria can play an important role in the pathogenesis of endothelial dysfunction [79,80]. Moreover, it has been shown that periodontal bacteria are able to directly induce the up-regulation of several adhesion and chemoattractant molecules of endothelial origin that stimulates the attachment of leukocytes onto the surface of endothelial cells [81–83]. For instance, *Porphyromonas gingivalis* can induce a robust expression of the endothelial monocyte chemoattractant protein-1 (MCP-1) [84]. Similarly, Nakamura and colleagues demonstrated that the activation of *Porphyromonas gingivalis*, via lipopolysaccharide (LPS)-TLR2 system, mediated the adhesion of monocytes to endothelial cells [85]. In addition to these effects, Ansai and colleagues demonstrated that, in gingival epithelial cells, *Porphyromonas gingivalis*, can induce a significant rise in endothelin-1 expression and release [86]. Importantly, ET-1 acts as a vasoconstrictor factor and high levels of this molecule are associated with the onset of CVD [87]. In line with this body of evidence, it has been demonstrated that periodontal treatment alone or supplementation with antibiotics is able to improve endothelial dysfunction [88–90].

In this regard, a recent meta-analysis has demonstrated the beneficial effects of periodontal therapy on endothelial function [91]. More in detail, in their analysis, Orlandi and coworkers observed that periodontal disease was associated with greater carotid intima-media thickness (c-IMT) and with impaired flow-mediated dilation (FMD), indicating the presence of atherosclerosis and endothelial dysfunction, respectively. Nevertheless, in patients that have undergone intensive periodontal treatments, the analysis demonstrated a substantial improvement in the gingival condition associated with an increased FMD [91].

In line with these reports, Houcken and colleagues have demonstrated that periodontal disease is associated with increased arterial stiffness, as seen by augmented pulse wave velocity (PWV), therefore displaying higher atherosclerotic risk [92]. Importantly, while in this study, periodontal treatment did not result in reduced PWV [92] and in the report by Vidal and colleagues, periodontal therapy was able to attenuate arterial stiffness and reduce circulating inflammatory markers [93].

#### 4.3. Peripheral Artery Disease (PAD)

PAD in its most advanced form, critical limb ischemia, represents a major health problem [94]. Importantly, a recent meta-analysis by Yang and colleagues demonstrated that PAD patients presented a higher risk of developing periodontitis compared to non-PAD subjects [95]. Moreover, these authors have observed that PAD patients have more missing teeth than non-PAD individuals. Importantly, this finding is in line with previous reports focused on this relationship. For instance, Chen and colleagues evaluated patients with PAD who underwent bypass surgery and reported that the majority of these patients presented periodontal bacterial infection (*Porphyromonas gingivalis*) of an anastomotic site of distal bypasses [96]. Interestingly, after adjusting for age, gender, smoking and DM, the authors found that periodontal disease increased up to five times the risk of developing PAD [96]. Furthermore, Ahn and coworkers [97] reported that patients with periodontitis had about a two-fold increase in the risk of PAD. In line with this observation, Çalapkörür and colleagues showed that periodontitis raised the odds ratio for developing PAD [98].

Importantly, due to the limited number of reports that have found a correlation between PAD and periodontitis, further studies with specific inclusion and exclusion criteria are required to confirm this relationship.

#### 4.4. Stroke

Stroke is one of the most common causes of mortality worldwide [99]. Although, many risk factors have been identified as for the onset of this pathology, which includes pre-existing heart disease, hypertension, dyslipidemia, DM, smoking and age [99,100], several epidemiological studies (cross-sectional, cohort and case-control studies) have suggested periodontitis as a major potential cause of stroke [101]. Indeed, a number of recent meta-analyses and systematic reviews have demonstrated that the risk of cerebral ischemia and stroke is higher in subjects with periodontitis [17,18,102,103]. Of note, oral dysbiosis appears to be central in this association. For instance, Pussinen and colleagues observed that an elevated level of serum antibody to *Aggregatibacter actinomycetemcomitans* and *Porphyromonas gingivalis* correlated with stroke [104]. Moreover, Ghizoni and coworkers demonstrated that patients with stroke presented periodontitis at dental sites, with deep pockets, contaminated by *Porphyromonas gingivalis* [105]. Finally, similarly to other CVDs, Hosomi and colleagues found an association between serum C-reactive protein levels, and that the presence of antibody against *Porphyromonas gingivalis* is significantly associated with acute ischemic stroke [106].

#### 4.5. Heart Failure

Heart failure (HF) is one of the leading causes of morbidity and mortality worldwide [99,107]. Importantly, its development is a consequence of many CVDs [99,107,108]. To date, only three studies have considered a potential relationship between periodontitis and HF [109–111]. In this regard, Fröhlich and colleagues observed that HF-patients had a higher prevalence of periodontitis [109]. However, in their study, the authors found that the severity of periodontitis was not associated with HF etiology and symptom severity [109]. In contrast, Wood and Johnson suggested an association between these diseases [110]. In particular, they observed that patients with periodontal disease had a higher rate of HF development. Interestingly, these authors demonstrated that the monthly consumption of anti-oxidant and anti-inflammatory molecules contained in tomato, such as lycopene and carotenoids, exerted a protective effect in HF patients [110]. Finally, in a recent cross-sectional study, Schulze-Späte and colleagues found that HF was associated with periodontitis [111]. Indeed, HF patients exhibited more severe periodontitis that was associated with increased bone turnover markers compared with control patients. Interestingly, the authors suggested that local and systemic factors, including inflammatory mediators and cytokines may account for this relationship [111].

### 5. Mechanistic Model for the Relationship Between Periodontal Disease and CVD

Although in clinical settings a potentially deep relationship between CVD and periodontitis has been observed, the detailed mechanism that connects these two pathologies has not been clarified yet. Nevertheless, oral pathogen dissemination into the bloodstream appears to be the major mechanism explaining such a relationship (Figure 1). For instance, bacteremia, often caused by non-surgical and surgical dental procedures, represents one of the major culprits of infective endocarditis in subjects predisposed to cardiac disease [112]. For this reason, prophylaxis is prescribed to patients with cardiac disease undergoing dental procedures [112].

Notably, periodontal pathogens can directly invade several organs and tissues, including the cardiovascular system. Accordingly, Louhelainen and colleagues recently reported that, in the pericardial fluids of patients with pericarditis, more than half (~60%) were positive for endodontitis-related bacteria while the remaining cohort (~40% of patients) were positive for periodontal pathogens [6]. Analogously, Oliveira and coworkers observed that periodontal pathogens were present in cardiac valve tissue of patients with valve disease [113]. Moreover, Ziebold and

colleagues also demonstrated the presence of the DNA of oral bacteria in both atrial and ventricular tissues in patients that underwent aortic valve surgery [13].

Mechanistically, in pre-clinical studies, Sekinishi and coworkers demonstrated that, in mice undergoing transverse aortic constriction (TAC), the injection of *Aggregatibacter actinomycetemcomitans* (a periodontal pathogen) induced a significant cardiac function deterioration, compared to controls (TAC mice injected with PBS). This effect was accompanied by an augmented cardiac fibrosis and hypertrophy, and an enhanced atherosclerosis [114]. Interestingly, the *Aggregatibacter actinomycetemcomitans* infection resulted in a significantly increased MMP-2 expression in the interstitial tissue [114]. Importantly, MMPs are well recognized factors activated by periodontal pathogens, involved in both physiological tissue remodeling and in pathological extracellular matrix (ECM) degradation, mechanisms that are part of the pathogenesis of periodontitis [31].

Of note, other reports have demonstrated that periodontal pathogens are also able to invade arterial walls and colonize atherosclerotic plaques [115–118]. In particular, recent data demonstrated that *Porphyromonas gingivalis*, one of the major pathogens involved in periodontal disease, induced platelets aggregation and the expression of several cell adhesion molecules, such as the intercellular adhesion molecule 1 (ICAM-1), the vascular cell adhesion molecule 1 (VCAM-1) and p-selectin. Moreover, Li and colleagues reported that the protease Gingipain R, released from *Porphyromonas gingivalis* caused CVD by activating protein C, factor X and prothrombin. These mechanisms of action lead to aggregation of platelets and thrombotic clot formation [119]. Of note, systemic dissemination of periodontal pathogens and/or endotoxins can induce an inflammatory response, both locally and systemically. In this regard, once in circulation, these microorganisms target large arteries, thus leading to the enhancement of vascular smooth muscle cells function, which represent one of the features of atherogenesis. Moreover, subsequent to bacterial infection, there is an augmented concentration of inflammatory mediators such as CRP [120], which has been proposed also as a potential risk factor for CVD development [121].

Finally, recent studies have indicated that chronic oral infection induces a high proportion of heat shock protein (HSP) 65 that increases the risk of CV events [122,123].

Despite all this evidence, more studies are needed, particularly in the experimental setting, to better understand and clarify the relationship between CVD and periodontitis.

## 6. Conclusions

In this review, we explored the potential association between periodontal disease and CVDs. Similarly, we described how periodontitis and diabetes were connected. Hence, the aim of this study was to increase the awareness among both clinicians and scientists about the need for a broader understanding of how periodontal disease prevention can impact CVD and diabetes. Doing so will not only provide additional preventative measures for CVDs, but also lower the economic burden on the health system. For this reason, effective health policy should focus on periodontitis as a CVD-related risk factor, due to the importance of preventing and treating all chronic infections.

Thus, in combination with diet, exercise and smoking control, preventing periodontal interventions should be in fact enlisted as an integral part of any adult health program directed to prevent, or more effectively manage CVD [124,125].

**Author Contributions:** D.L., A.C. (Alessandro Cannavo), G.R., G.S. and C.R. designed, wrote and revised the manuscript. N.F. and A.C. (Antonio Cittadini) revised the manuscript.

**Funding:** This research was partly funded by: STAR program 2016 L1—Compagnia San Paolo and Federico II University of Naples (to G.R.); STAR program 2017 L1—Compagnia San Paolo and Federico II University of Naples (to Alessandro Cannavo.); Italian Ministry of Education, Universities and Research—“Rita Levi Montalcini 2016” (to Alessandro Cannavo).

**Conflicts of Interest:** The authors declare no conflicts of interest.

## Abbreviations

CVD	Cardiovascular Disease
IL	Interleukin
PGE2	Prostaglandin E2
TNF	Tumor Necrosis Factor
MMP	Matrix Metalloproteinase
PAD	Peripheral Artery Disease
HF	Heart Failure
DM	Diabetes Mellitus
HSP	Heat shock protein
CRP	C-reactive protein

## References

1. Nazir, M.A. Prevalence of periodontal disease, its association with systemic diseases and prevention. *Int. J. Health Sci. (Qassim)* **2017**, *11*, 72–80.
2. Sudhakara, P.; Gupta, A.; Bhardwaj, A.; Wilson, A. Oral Dysbiotic Communities and Their Implications in Systemic Diseases. *Dent. J. (Basel)* **2018**, *6*, 10. [[CrossRef](#)] [[PubMed](#)]
3. Jin, J.; Zhang, X.; Lu, Z.; Li, Y.; Lopes-Virella, M.F.; Yu, H.; Haycraft, C.J.; Li, Q.; Kirkwood, K.L.; Huang, Y. Simvastatin inhibits lipopolysaccharide-induced osteoclastogenesis and reduces alveolar bone loss in experimental periodontal disease. *J. Periodontol. Res.* **2014**, *49*, 518–526. [[CrossRef](#)] [[PubMed](#)]
4. Neely, A.L.; Holford, T.R.; Loe, H.; Anerud, A.; Boysen, H. The natural history of periodontal disease in humans: Risk factors for tooth loss in caries-free subjects receiving no oral health care. *J. Clin. Periodontol.* **2005**, *32*, 984–893. [[CrossRef](#)]
5. Monsarrat, P.; Blaizot, A.; Kémoun, P.; Ravaud, P.; Nabet, C.; Sixou, M.; Vergnes, J.N. Clinical research activity in periodontal medicine: A systematic mapping of trial registers. *J. Clin. Periodontol.* **2016**, *43*, 390–400. [[CrossRef](#)] [[PubMed](#)]
6. Louhelainen, A.M.; Aho, J.; Tuomisto, S.; Aittoniemi, J.; Vuento, R.; Karhunen, P.J.; Pessi, T. Oral bacterial DNA findings in pericardial fluid. *J. Oral Microbiol.* **2014**, *6*, 25835. [[CrossRef](#)]
7. Nakano, K.; Inaba, H.; Nomura, R.; Nemoto, H.; Takeda, M.; Yoshioka, H.; Matsue, H.; Takahashi, T.; Taniguchi, K.; Amano, A.; et al. Detection of cariogenic Streptococcus mutans in extirpated heart valve and atheromatous plaque specimens. *J. Clin. Microbiol.* **2006**, *44*, 3313–3317. [[CrossRef](#)]
8. Moreno, S.; Parra, B.; Botero, J.E.; Moreno, F.; Vásquez, D.; Fernández, H.; Alba, S.; Gallego, S.; Castillo, G.; Contreras, A. Periodontal microbiota and microorganisms isolated from heart valves in patients undergoing valve replacement surgery in a clinic in Cali, Colombia. *Biomedica* **2017**, *37*, 516–525. [[CrossRef](#)] [[PubMed](#)]
9. Kozarov, E.; Sweier, D.; Shelburne, C.; Progulske-Fox, A.; Lopatin, D. Detection of bacterial DNA in atheromatous plaques by quantitative PCR. *Microbes Infect.* **2006**, *8*, 687–693. [[CrossRef](#)] [[PubMed](#)]
10. Cavrini, F.; Sambri, V.; Moter, A.; Servidio, D.; Marangoni, A.; Montebugnoli, L.; Foschi, F.; Prati, C.; Di Bartolomeo, R.; Cevenini, R. Molecular detection of Treponema denticola and Porphyromonas gingivalis in carotid and aortic atheromatous plaques by fish: Report of two cases. *J. Med. Microbiol.* **2005**, *54*, 93–96. [[CrossRef](#)] [[PubMed](#)]
11. Okuda, K.; Ishihara, K.; Nakagawa, T.; Hirayama, A.; Inayama, Y. Detection of Treponema denticola in atherosclerotic lesions. *J. Clin. Microbiol.* **2001**, *39*, 1114–1117. [[CrossRef](#)]
12. Marcelino, S.L.; Gaetti-Jardim, E.; Nakano, V.; Canônico, L.A.; Nunes, F.D.; Lotufo, R.F.; Pustiglioni, F.E.; Romito, G.A.; Avila-Campos, M.J.; Pessi, T.; et al. Bacterial signatures in thrombus aspirates of patients with myocardial infarction. *Circulation* **2013**, *127*, 1219–1228.
13. Ziebolz, D.; Jahn, C.; Pegel, J.; Semper-Pinnecke, E.; Mausberg, R.F.; Waldmann-Beushausen, R.; Schöndube, F.A.; Danner, B.C. Periodontal bacteria DNA findings in human cardiac tissue—Is there a link of periodontitis to heart valve disease? *Int. J. Cardiol.* **2018**, *251*, 74–79. [[CrossRef](#)]
14. Genco, R.J.; Grossi, S.G.; Ho, A.; Nishimura, F.; Murayama, Y. A proposed model linking inflammation to obesity, diabetes, and periodontal infections. *J. Periodontol.* **2005**, *76*, 2075–2084. [[CrossRef](#)] [[PubMed](#)]
15. Beck, J.D.; Offenbacher, S. Systemic effects of periodontitis: Epidemiology of periodontal disease and cardiovascular disease. *J. Periodontol.* **2005**, *76*, 2089–2100. [[CrossRef](#)] [[PubMed](#)]



16. Carrizales-Sepúlveda, E.F.; Ordaz-Farías, A.; Vera-Pineda, R.; Flores-Ramírez, R. Periodontal Disease, Systemic Inflammation and the Risk of Cardiovascular Disease. *Heart Lung Circ.* **2018**, *27*, 1327–1334. [[CrossRef](#)]
17. Janket, S.-J.; Baird, A.; Chuang, S.; Jones, J.A. Meta-analysis of periodontal disease and risk of coronary heart disease and stroke. *Oral Surg. Oral Med. Oral Pathol. Oral Radiol. Endodontol.* **2003**, *95*, 559–569. [[CrossRef](#)] [[PubMed](#)]
18. Khader, Y.S.; Albashaireh, Z.S.M.; Alomari, M.A. Periodontal diseases and the risk of coronary heart and cerebrovascular diseases: A meta-analysis. *J. Periodontol.* **2004**, *75*, 1046–1153. [[CrossRef](#)] [[PubMed](#)]
19. Seymour, G.J.; Ford, P.J.; Cullinan, M.P.; Leishman, S.; Yamazaki, K. Relationship between periodontal infections and systemic disease. *Clin. Microbiol. Infect.* **2007**, *13* (Suppl. 4), 3–10. [[CrossRef](#)]
20. Santos, C.M.; Lira-Junior, R.; Fischer, R.G.; Santos, A.P.; Oliveira, B.H. Systemic Antibiotics in Periodontal Treatment of Diabetic Patients: A Systematic Review. *PLoS ONE* **2015**, *10*, e0145262. [[CrossRef](#)] [[PubMed](#)]
21. Guzman, S.; Karima, M.; Wang, H.Y.; van Dyke, T.E. Association between interleukin—1 genotype and periodontal disease in a diabetic population. *J. Periodontol.* **2003**, *74*, 1183–1190. [[CrossRef](#)] [[PubMed](#)]
22. Tsai, C.; Hayes, C.; Taylor, G.W. Glycemic control of type 2 diabetes and severe periodontal disease in the US adult population. *Community Dent. Oral Epidemiol.* **2002**, *30*, 182–192. [[CrossRef](#)] [[PubMed](#)]
23. Darveau, R.P. Periodontitis: A polymicrobial disruption of host homeostasis. *Nat. Rev. Microbiol.* **2010**, *8*, 481–490. [[CrossRef](#)] [[PubMed](#)]
24. Slots, J. Periodontology: Past, present, perspectives. *Periodontol 2000* **2013**, *62*, 7–19. [[CrossRef](#)]
25. Lourenco, T.G.; Heller, D.; Silva-Boghossian, C.M.; Cotton, S.L.; Paster, B.J.; Colombo, A.P. Microbial signature profiles of periodontally healthy and diseased patients. *J. Clin. Periodontol.* **2014**, *41*, 1027–1036. [[CrossRef](#)] [[PubMed](#)]
26. Shaddox, L.M.; Huang, H.; Lin, T.; Hou, W.; Harrison, P.L.; Aukhil, I.; Walker, C.B.; Klepac-Ceraj, V.; Paster, B.J. Microbiological Characterization in Children with Aggressive Periodontitis. *J. Dent. Res.* **2012**, *91*, 927–933. [[CrossRef](#)] [[PubMed](#)]
27. Zadeh, H.H.; Nichols, F.C.; Miyasaki, K.T. The role of the cell-mediated immune response to *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis* in periodontitis. *Periodontol 2000* **1999**, *20*, 239–242. [[CrossRef](#)] [[PubMed](#)]
28. Hasturk, H.; Kantarci, A. Activation and resolution of periodontal inflammation and its systemic impact. *Periodontol 2000.* **2015**, *69*, 255–273. [[CrossRef](#)] [[PubMed](#)]
29. Cekici, A.; Kantarci, A.; Hasturk, H.; Van Dyke, T.E. Inflammatory and immune pathways in the pathogenesis of periodontal disease. *Periodontol 2000* **2014**, *64*, 57–80. [[CrossRef](#)]
30. Hajishengallis, G. Immunomicrobial pathogenesis of periodontitis: Keystones, pathobionts, and host response. *Trends Immunol.* **2014**, *35*, 3–11. [[CrossRef](#)]
31. Franco, C.; Patricia, H.R.; Timo, S.; Claudia, B.; Marcela, H. Matrix Metalloproteinases as Regulators of Periodontal Inflammation. *Int. J. Mol. Sci.* **2017**, *18*, 440. [[CrossRef](#)] [[PubMed](#)]
32. Rengo, G.; Pagano, G.; Paolillo, S.; de Lucia, C.; Femminella, G.D.; Liccardo, D.; Cannavo, A.; Formisano, R.; Petraglia, L.; Komici, K.; et al. Impact of diabetes mellitus on lymphocyte GRK2 protein levels in patients with heart failure. *Eur. J. Clin. Investig.* **2015**, *45*, 187–195. [[CrossRef](#)] [[PubMed](#)]
33. Belting, S.M.; Hiniker, J.J.; Dummett, C.O. Influence of diabetes mellitus on the severity of periodontal disease. *J. Periodontol.* **1964**, *35*, 476–480. [[CrossRef](#)]
34. Blasco-Baque, V.; Garidou, L.; Pomié, C.; Escoula, Q.; Loubieres, P.; Le Gall-David, S.; Lemaitre, M.; Nicolas, S.; Klopp, P.; Waget, A.; et al. Periodontitis induced by *Porphyromonas gingivalis* drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response. *Gut* **2017**, *66*, 872–885. [[PubMed](#)]
35. Liu, Y.; Zhang, Q.J. Periodontitis aggravated pancreatic  $\beta$ -cell dysfunction in diabetic mice through interleukin-12 regulation on Klotho. *Diabetes Investig.* **2016**, *7*, 303–311. [[CrossRef](#)]
36. Engebretson, S.; Kocher, T. Evidence that periodontal treatment improves diabetes outcomes: A systematic review and meta-analysis. *J. Clin. Periodontol.* **2013**, *40*, S153–S163. [[CrossRef](#)] [[PubMed](#)]
37. Teshome, A.; Yitayeh, A. The effect of periodontal therapy on glycemic control and fasting plasma glucose level in type 2 diabetic patients: Systematic review and meta-analysis. *BMC Oral Health* **2016**, *17*, 31. [[CrossRef](#)] [[PubMed](#)]

38. Faggion, C.M., Jr.; Cullinan, M.P.; Atieh, M. An overview of systematic reviews on the effectiveness of periodontal treatment to improve glycaemic control. *J. Periodontol. Res.* **2016**, *51*, 716–725. [[CrossRef](#)] [[PubMed](#)]
39. Artese, H.P.; Foz, A.M.; Rabelo Mde, S.; Gomes, G.H.; Orlandi, M.; Suvan, J.; D’Aiuto, F.; Romito, G.A. Periodontal therapy and systemic inflammation in type 2 diabetes mellitus: A meta-analysis. *PLoS ONE* **2015**, *10*, e0128344. [[CrossRef](#)]
40. De Miguel-Infante, A.; Martínez-Huedo, M.A.; Mora-Zamorano, E.; Hernández-Barrera, V.; Jiménez-Trujillo, I.; de Burgos-Lunar, C.; Cardenas Valladolid, J.; Jiménez-García, R.; Lopez-de-Andrés, A. Periodontal disease in adults with diabetes, prevalence and risk factors. Results of an observational study. *Int. J. Clin. Pract.* **2018**, e13294. [[CrossRef](#)]
41. Salvi, G.E.; Kandyliaki, M.; Troendle, A.; Persson, G.R.; Lang, N.P. Experimental gingivitis in type 1 diabetics: A controlled clinical and microbiological study. *J. Clin. Periodontol.* **2005**, *32*, 310–316. [[CrossRef](#)] [[PubMed](#)]
42. Ardakani, M.R.; Moeintaghavi, A.; Haerian, A.; Ardakani, M.A.; Hashemzadeh, M. Correlation between levels of sulcular and capillary blood glucose. *J. Contemp. Dent. Pract.* **2009**, *10*, 10–17.
43. Sakallioğlu, E.E.; Lutfioğlu, M.; Sakallioğlu, U.; Diraman, E.; Keskiner, I. Fluid dynamics of gingiva in diabetic and systemically healthy periodontitis patients. *Arch. Oral Biol.* **2008**, *53*, 646–651. [[CrossRef](#)]
44. Salvi, G.E.; Franco, L.M.; Braun, T.M.; Lee, A.; Persson, G.R.; Lang, N.P.; Giannobile, W.V. Pro-inflammatory biomarkers during experimental gingivitis in patients with type 1 diabetes mellitus: A proof-of-concept study. *J. Clin. Periodontol.* **2010**, *37*, 9–16. [[CrossRef](#)] [[PubMed](#)]
45. Engebretson, S.; Chertog, R.; Nichols, A.; Hey-Hadavi, J.; Celenti, R.; Grbic, J. Plasma levels of tumour necrosis factor-alpha in patients with chronic periodontitis and type 2 diabetes. *J. Clin. Periodontol.* **2007**, *34*, 18–24. [[CrossRef](#)] [[PubMed](#)]
46. Noack, B.; Genco, R.J.; Trevisan, M.; Grossi, S.; Zambon, J.J.; de Nardin, E. Periodontal infections contribute to elevated systemic C-reactive protein level. *J. Periodontol.* **2001**, *72*, 1221–1227. [[CrossRef](#)]
47. Loos, B.G.; Craandijk, J.; Hoek, F.J.; Wertheim-van Dillen, P.M.E.; van der Velden, U. C-reactive protein and other markers of systemic inflammation in relation to cardiovascular diseases are elevated in periodontitis. *J. Periodontol.* **2000**, *71*, 1528–1534. [[CrossRef](#)] [[PubMed](#)]
48. Wu, T.; Trevisan, M.; Genco, R.J.; Falkner, K.L.; Dorn, J.P.; Sempos, C.T. Examination of the relation between periodontal health status and cardiovascular risk factors: Serum total and high density lipoprotein cholesterol, C-reactive protein, and plasma fibrinogen. *Am. J. Epidemiol.* **2000**, *151*, 273–282. [[CrossRef](#)] [[PubMed](#)]
49. Chen, L.; Wei, B.; Li, J.; Liu, F.; Xuan, D.; Xie, B.; Zhang, J. Association of periodontal parameters with metabolic level and systemic inflammatory markers in patients with type 2 diabetes. *J. Periodontol.* **2010**, *81*, 364–371. [[CrossRef](#)]
50. Chen, L.; Luo, G.; Xuan, D.; Wei, B.; Liu, F.; Li, J.; Zhang, J. Effects of non-surgical periodontal treatment on clinical response, serum inflammatory parameters, and metabolic control in patients with type 2 diabetes: A randomized study. *J. Periodontol.* **2012**, *83*, 435–443. [[CrossRef](#)]
51. Quintero, A.J.; Chaparro, A.; Quirynen, M.; Ramirez, V.; Prieto, D.; Morales, H.; Prada, P.; Hernández, M.; Sanz, A. Effect of two periodontal treatment modalities in patients with uncontrolled type 2 diabetes mellitus: A randomized clinical trial. *J. Clin. Periodontol.* **2018**, *45*, 1098–1106. [[CrossRef](#)]
52. Grellmann, A.P.; Sfreddo, C.S.; Maier, J.; Lenzi, T.L.; Zanatta, F.B. Systemic antimicrobials adjuvant to periodontal therapy in diabetic subjects: A meta-analysis. *J. Clin. Periodontol.* **2016**, *43*, 250–260. [[CrossRef](#)]
53. Lira Junior, R.; Santos, C.M.M.; Oliveira, B.H.; Fischer, R.G.; Santos, A.P.P. Effects on HbA1c in diabetic patients of adjunctive use of systemic antibiotics in nonsurgical periodontal treatment: A systematic review. *J. Dent.* **2017**, *66*, 1–7. [[CrossRef](#)] [[PubMed](#)]
54. Patil, V.S.; Patil, V.P.; Gokhale, N.; Acharya, A.; Kangokar, P. Chronic Periodontitis in Type 2 Diabetes Mellitus: Oxidative Stress as a Common Factor in Periodontal Tissue Injury. *J. Clin. Diagn. Res.* **2016**, *10*, BC12–BC16. [[CrossRef](#)]
55. Allen, E.M.; Matthews, J.B.; O’Halloran, D.J.; Griffiths, H.R.; Chapple, I.L. Oxidative and inflammatory status in Type 2 diabetes patients with periodontitis. *J. Clin. Periodontol.* **2011**, *38*, 894–901. [[CrossRef](#)] [[PubMed](#)]
56. Polak, D.; Shapira, L. An update on the evidence for pathogenic mechanisms that may link periodontitis and diabetes. *J. Clin. Periodontol.* **2018**, *45*, 150–166. [[CrossRef](#)] [[PubMed](#)]

57. Kjellström, B.; Gustafsson, A.; Nordendal, E.; Norhammar, A.; Nygren, Å.; Näsman, P.; Rydén, L.; Åsberg, M. PAROKRANK steering committee. Symptoms of depression and their relation to myocardial infarction and periodontitis. *Eur. J. Cardiovasc. Nurs.* **2017**, *16*, 468–474. [[CrossRef](#)] [[PubMed](#)]
58. De Nardin, E. The role of inflammatory and immunological mediators in periodontitis and cardiovascular disease. *Ann. Periodontol.* **2001**, *6*, 30–40. [[CrossRef](#)] [[PubMed](#)]
59. Shrihari, T.G. Potential correlation between periodontitis and coronary heart disease—an overview. *Gen. Dent.* **2012**, *60*, 20–24.
60. Woźakowska-Kapłon, B.; Włosowicz, M.; Gorczyca-Michta, I.; Górska, R. Oral health status and the occurrence and clinical course of myocardial infarction in hospital phase: A case-control study. *Cardiol. J.* **2013**, *20*, 370–377. [[CrossRef](#)]
61. Kodovazenitis, G.; Pitsavos, C.; Papadimitriou, L.; Vrotsos, I.A.; Stefanadis, C.; Madianos, P.N. Association between periodontitis and acute myocardial infarction: A case-control study of a nondiabetic population. *J. Periodontal Res.* **2014**, *49*, 246–252. [[CrossRef](#)] [[PubMed](#)]
62. Noguchi, S.; Toyokawa, S.; Miyoshi, Y.; Suyama, Y.; Inoue, K.; Kobayashi, Y. Five-year follow-up study of the association between periodontal disease and myocardial infarction among Japanese male workers: MY Health Up Study. *J. Public Health (Oxf.)* **2015**, *37*, 605–611. [[CrossRef](#)] [[PubMed](#)]
63. Rydén, L.; Buhlin, K.; Ekstrand, E.; de Faire, U.; Gustafsson, A.; Holmer, J.; Kjellström, B.; Lindahl, B.; Norhammar, A.; Nygren, Å.; et al. Periodontitis Increases the Risk of a First Myocardial Infarction: A Report From the PAROKRANK Study. *Circulation* **2016**, *133*, 576–578. [[PubMed](#)]
64. Mattila, K.J.; Nieminen, M.S.; Valtonen, V.V.; Rasi, V.P.; Kesäniemi, Y.A.; Syrjälä, S.L.; Jungell, P.S.; Isoluoma, M.; Hietaniemi, K.; Jokinen, M.J. Association between dental health and acute myocardial infarction. *BMJ* **1989**, *298*, 779–781. [[CrossRef](#)]
65. Willershausen, B.; Kasaj, A.; Willershausen, I.; Zahorka, D.; Briseño, B.; Blettner, M.; Genth-Zotz, S.; Münzel, T. Association between chronic dental infection and acute myocardial infarction. *J. Endod.* **2009**, *35*, 626–630. [[CrossRef](#)] [[PubMed](#)]
66. Jansson, L.; Lavstedt, S.; Frithiof, L.; Theobald, H. Relationship between oral health and mortality in cardiovascular diseases. *J. Clin. Periodontol.* **2001**, *28*, 762–768. [[CrossRef](#)]
67. Akamatsu, Y.; Yamamoto, T.; Yamamoto, K.; Oseko, F.; Kanamura, N.; Imanishi, J.; Kita, M. Porphyromonas gingivalis induces myocarditis and/or myocardial infarction in mice and IL-17A is involved in pathogenesis of these diseases. *Arch. Oral Biol.* **2011**, *56*, 1290–1298. [[CrossRef](#)] [[PubMed](#)]
68. Hujuel, P.P.; Drangsholt, M.; Spiekerman, C.; Derouen, T.A. Examining the link between coronary heart disease and the elimination of chronic dental infections. *J. Am. Dent. Assoc.* **2001**, *132*, 883–889. [[CrossRef](#)]
69. Howell, T.H.; Ridker, P.M.; Ajani, U.A.; Hennekens, C.H.; Christen, W.G. Periodontal disease and risk of subsequent cardiovascular disease in U.S. male physicians. *J. Am. Coll. Cardiol.* **2001**, *37*, 445–450. [[CrossRef](#)]
70. Sidhu, R.K. Association between Acute Myocardial Infarction and Periodontitis: A Review of the Literature. *J. Int. Acad. Periodontol.* **2016**, *18*, 23–33.
71. Lockhart, P.B.; Bolger, A.F.; Papapanou, P.N.; Osinbowale, O.; Trevisan, M.; Levison, M.E.; Taubert, K.A.; Newburger, J.W.; Gornik, H.L.; Gewitz, M.H.; et al. American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Periodontal disease and atherosclerotic vascular disease: Does the evidence support an independent association? A scientific statement from the American Heart Association. *Circulation* **2012**, *125*, 2520–2544. [[PubMed](#)]
72. Park, K.H.; Park, W.J. Endothelial Dysfunction: Clinical Implications in Cardiovascular Disease and Therapeutic Approaches. *J. Korean Med. Sci.* **2015**, *30*, 1213–1225. [[CrossRef](#)] [[PubMed](#)]
73. Radomski, M.W.; Palmer, R.M.; Moncada, S. Comparative pharmacology of endothelium-derived relaxing factor, nitric oxide and prostacyclin in platelets. *Br. J. Pharmacol.* **1987**, *92*, 181. [[CrossRef](#)] [[PubMed](#)]
74. Garg, U.C.; Hassid, A. Nitric oxide-generating vasodilators and 8-bromo-cyclic guanosine monophosphate inhibit mitogenesis and proliferation of cultured rat vascular smooth muscle cells. *J. Clin. Investig.* **1989**, *83*, 1774. [[CrossRef](#)] [[PubMed](#)]
75. Higashi, Y.; Goto, C.; Jitsuiki, D.; Umemura, T.; Nishioka, K.; Hidaka, T.; Takemoto, H.; Nakamura, S.; Soga, J.; Chayama, K.; et al. Periodontal infection is associated with endothelial dysfunction in healthy subjects and hypertensive patients. *Hypertension* **2008**, *51*, 446–453. [[CrossRef](#)] [[PubMed](#)]

76. Moura, M.F.; Navarro, T.P.; Silva, T.A.; Cota, L.O.M.; Soares Dutra Oliveira, A.M.; Costa, F.O. Periodontitis and Endothelial Dysfunction: Periodontal Clinical Parameters and Levels of Salivary Markers Interleukin-1 $\beta$ , Tumor Necrosis Factor- $\alpha$ , Matrix Metalloproteinase-2, Tissue Inhibitor of Metalloproteinases-2 Complex, and Nitric Oxide. *J. Periodontol.* **2017**, *88*, 778–787. [[CrossRef](#)] [[PubMed](#)]
77. Brito, L.C.; DalBó, S.; Striechen, T.M.; Farias, J.M.; Olchanheski, L.R., Jr.; Mendes, R.T.; Velloso, J.C.; Fávero, G.M.; Sordi, R.; Assreuy, J.; et al. Experimental periodontitis promotes transient vascular inflammation and endothelial dysfunction. *Arch. Oral Biol.* **2013**, *58*, 1187–1198. [[CrossRef](#)] [[PubMed](#)]
78. Campi, P.; Herrera, B.S.; de Jesus, F.N.; Napolitano, M.; Teixeira, S.A.; Maia-Dantas, A.; Spolidorio, L.C.; Akamine, E.H.; Mayer, M.P.A.; de Carvalho, M.H.C.; et al. Endothelial dysfunction in rats with ligature-induced periodontitis: Participation of nitric oxide and cyclooxygenase-2-derived products. *Arch. Oral Biol.* **2016**, *63*, 66–74. [[CrossRef](#)]
79. Maekawa, T.; Takahashi, N.; Honda, T.; Yonezawa, D.; Miyashita, H.; Okui, T.; Tabeta, K.; Yamazaki, K. Porphyromonas gingivalis antigens and interleukin-6 stimulate the production of monocyte chemoattractant protein-1 via the upregulation of early growth response-1 transcription in human coronary artery endothelial cells. *J. Vasc. Res.* **2010**, *47*, 346–354. [[CrossRef](#)]
80. Bhagat, K.; Moss, R.; Collier, J.; Vallance, P. Endothelial “stunning” following a brief exposure to endotoxin: A mechanism to link infection and infarction? *Cardiovasc. Res.* **1996**, *32*, 822–829.
81. Hajishengallis, G.; Wang, M.; Harokopakis, E.; Triantafilou, M.; Triantafilou, K. Porphyromonas gingivalis fimbriae proactively modulate beta2 integrin adhesive activity and promote binding to and internalization by macrophages. *Infect. Immun.* **2006**, *74*, 5658–5666. [[CrossRef](#)] [[PubMed](#)]
82. Roth, G.A.; Moser, B.; Roth-Walter, F.; Giacona, M.B.; Harja, E.; Papapanou, P.N.; Schmidt, A.M.; Lalla, E. Infection with a periodontal pathogen increases mononuclear cell adhesion to human aortic endothelial cells. *Atherosclerosis* **2007**, *190*, 271–281. [[CrossRef](#)]
83. Hashizume, T.; Kurita-Ochiai, T.; Yamamoto, M. Porphyromonas gingivalis stimulates monocyte adhesion to human umbilical vein endothelial cells. *FEMS Immunol. Med. Microbiol.* **2011**, *62*, 57–65. [[CrossRef](#)] [[PubMed](#)]
84. Niu, J.; Kolattukudy, P.E. Role of MCP-1 in cardiovascular disease: Molecular mechanisms and clinical implications. *Clin. Sci. (Lond.)* **2009**, *117*, 95–109. [[CrossRef](#)]
85. Nakamura, N.; Yoshida, M.; Umeda, M.; Huang, Y.; Kitajima, S.; Inoue, Y.; Ishikawa, I.; Iwai, T. Extended exposure of lipopolysaccharide fraction from Porphyromonas gingivalis facilitates mononuclear cell adhesion to vascular endothelium via Toll-like receptor-2 dependent mechanism. *Atherosclerosis* **2008**, *196*, 59–67. [[CrossRef](#)] [[PubMed](#)]
86. Ansai, T.; Yamamoto, E.; Awano, S.; Yu, W.; Turner, A.J.; Takehara, T. Effects of periodontopathic bacteria on the expression of endothelin-1 in gingival epithelial cells in adult periodontitis. *Clin. Sci. (Lond.)* **2002**, *103*, 327S–331S. [[CrossRef](#)] [[PubMed](#)]
87. Vanhoutte, P.M.; Shimokawa, H.; Feletou, M.; Tang, E.H. Endothelial dysfunction and vascular disease—a 30th anniversary update. *Acta Physiol. (Oxf.)* **2017**, *219*, 22–96. [[CrossRef](#)] [[PubMed](#)]
88. Seinost, G.; Wimmer, G.; Skerget, M.; Thaller, E.; Brodmann, M.; Gasser, R.; Bratschko, R.O.; Pilger, E. Periodontal treatment improves endothelial dysfunction in patients with severe periodontitis. *Am. Heart J.* **2005**, *149*, 1050–1054. [[CrossRef](#)] [[PubMed](#)]
89. Elter, J.R.; Hinderliter, A.L.; Offenbacher, S.; Beck, J.D.; Caughey, M.; Brodala, N.; Madianos, P.N. The effects of periodontal therapy on vascular endothelial function: A pilot trial. *Am. Heart J.* **2006**, *151*, 47. [[CrossRef](#)]
90. Tonetti, M.S.; D’Aiuto, F.; Nibali, L.; Donald, A.; Storry, C.; Parkar, M.; Suvan, J.; Hingorani, A.D.; Vallance, P.; Deanfield, J. Treatment of periodontitis and endothelial function. *N. Engl. J. Med.* **2007**, *356*, 911–920. [[CrossRef](#)] [[PubMed](#)]
91. Orlandi, M.; Suvan, J.; Petrie, A.; Donos, N.; Masi, S.; Hingorani, A.; Deanfield, J.; D’Aiuto, F. Association between periodontal disease and its treatment, flow-mediated dilatation and carotid intima-media thickness: A systematic review and meta-analysis. *Atherosclerosis* **2014**, *236*, 39–46. [[CrossRef](#)] [[PubMed](#)]
92. Houcken, W.; Teeuw, W.J.; Bizzarro, S.; Alvarez Rodriguez, E.; Mulders, T.A.; van den Born, B.J.; Loos, B.G. Arterial stiffness in periodontitis patients and controls. A case-control and pilot intervention study. *J. Hum. Hypertens.* **2016**, *30*, 24–29. [[CrossRef](#)] [[PubMed](#)]

93. Vidal, F.; Cordovil, I.; Figueredo, C.M.; Fischer, R.G. Non-surgical periodontal treatment reduces cardiovascular risk in refractory hypertensive patients: A pilot study. *J. Clin. Periodontol.* **2013**, *40*, 681–687. [[CrossRef](#)] [[PubMed](#)]
94. Cannavo, A.; Liccardo, D.; Lympelopoulou, A.; Gambino, G.; D'Amico, M.L.; Rengo, F.; Koch, W.J.; Leosco, D.; Ferrara, N.; Rengo, G.  $\beta$  Adrenergic Receptor Kinase C-Terminal Peptide Gene-Therapy Improves  $\beta$ 2-Adrenergic Receptor-Dependent Neoangiogenesis after Hindlimb Ischemia. *J. Pharmacol. Exp. Ther.* **2016**, *356*, 503–513. [[CrossRef](#)] [[PubMed](#)]
95. Yang, S.; Zhao, L.S.; Cai, C.; Shi, Q.; Wen, N.; Xu, J. Association between periodontitis and peripheral artery disease: A systematic review and meta-analysis. *BMC Cardiovasc. Disord.* **2018**, *18*, 141. [[CrossRef](#)]
96. Chen, Y.W.; Umeda, M.; Nagasawa, T.; Takeuchi, Y.; Huang, Y.; Inoue, Y.; Iwai, T.; Izumi, Y.; Ishikawa, I. Periodontitis may increase the risk of peripheral arterial disease. *Eur. J. Vasc. Endovasc. Surg.* **2008**, *35*, 153–158. [[CrossRef](#)] [[PubMed](#)]
97. Ahn, Y.B.; Shin, M.S.; Han, D.H.; Sukhbaatar, M.; Kim, M.S.; Shin, H.S.; Kim, H.D. Periodontitis is associated with the risk of subclinical atherosclerosis and peripheral arterial disease in Korean adults. *Atherosclerosis* **2016**, *251*, 311–318. [[CrossRef](#)] [[PubMed](#)]
98. Çalapkörür, M.U.; Alkan, B.A.; Tasdemir, Z.; Akcali, Y.; Saatçi, E. Association of peripheral arterial disease with periodontal disease: Analysis of inflammatory cytokines and an acute phase protein in gingival crevicular fluid and serum. *J. Periodontal Res.* **2017**, *52*, 532–539. [[CrossRef](#)]
99. Benjamin, E.J.; Muntner, P.; Alonso, A.; Bittencourt, M.S.; Callaway, C.W.; Carson, A.P.; Chamberlain, A.M.; Chang, A.R.; Cheng, S.; Das, S.R.; et al. American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation* **2019**, *139*, e56–e66. [[CrossRef](#)] [[PubMed](#)]
100. Kelly, B.M.; Pangilinan, P.H., Jr.; Rodriguez, G.M. The stroke rehabilitation paradigm. *Phys. Med. Rehabil. Clin. N. Am.* **2007**, *18*, 631–650. [[CrossRef](#)] [[PubMed](#)]
101. Leira, Y.; Seoane, J.; Blanco, M.; Rodríguez-Yáñez, M.; Takkouche, B.; Blanco, J.; Castillo, J. Association between periodontitis and ischemic stroke: A systematic review and meta-analysis. *Eur. J. Epidemiol.* **2017**, *32*, 43–53. [[CrossRef](#)] [[PubMed](#)]
102. Sfyroeras, G.S.; Roussas, N.; Saleptsis, V.G.; Argyriou, C.; Giannoukas, A.D. Association between periodontal disease and stroke. *J. Vasc. Surg.* **2012**, *55*, 1178–1184. [[CrossRef](#)] [[PubMed](#)]
103. Lafon, A.; Pereira, B.; Dufour, T.; Rigouby, V.; Giroud, M.; Béjot, Y.; Tubert-Jeannin, S. Periodontal disease and stroke: A meta-analysis of cohort studies. *Eur. J. Neurol.* **2014**, *21*, 1155–1161. [[CrossRef](#)] [[PubMed](#)]
104. Pussinen, P.J.; Alfthan, G.; Rissanen, H.; Reunanen, A.; Asikainen, S.; Knekt, P. Antibodies to periodontal pathogens and stroke risk. *Stroke* **2004**, *35*, 2020–2023. [[CrossRef](#)] [[PubMed](#)]
105. Ghizoni, J.S.; Taveira, L.A.; Garlet, G.P.; Ghizoni, M.F.; Pereira, J.R.; Dionísio, T.J.; Brozoski, D.T.; Santos, C.F.; Sant'Ana, A.C. Increased levels of Porphyromonas gingivalis are associated with ischemic and hemorrhagic cerebrovascular disease in humans: An in vivo study. *J. Appl. Oral Sci.* **2012**, *20*, 104–112. [[CrossRef](#)]
106. Hosomi, N.; Aoki, S.; Matsuo, K.; Deguchi, K.; Masugata, H.; Murao, K.; Ichihara, N.; Ohyama, H.; Dobashi, H.; Nezu, T.; et al. Association of serum anti-periodontal pathogen antibody with ischemic stroke. *Cerebrovasc. Dis.* **2012**, *34*, 385–392. [[CrossRef](#)]
107. Ponikowski, P.; Anker, S.D.; AlHabib, K.F.; Cowie, M.R.; Force, T.L.; Hu, S.; Jaarsma, T.; Krum, H.; Rastogi, V.; Rohde, L.E.; et al. Heart failure: Preventing disease and death worldwide. *ESC Heart Fail.* **2014**, *1*, 4–25. [[CrossRef](#)] [[PubMed](#)]
108. Cannavo, A.; Komici, K.; Bencivenga, L.; D'Amico, M.L.; Gambino, G.; Liccardo, D.; Ferrara, N.; Rengo, G. GRK2 as a therapeutic target for heart failure. *Expert Opin. Ther. Targets* **2018**, *22*, 75–83. [[CrossRef](#)] [[PubMed](#)]
109. Fröhlich, H.; Herrmann, K.; Franke, J.; Karimi, A.; Täger, T.; Cebola, R.; Katus, H.A.; Zugck, C.; Frankenstein, L. Periodontitis in Chronic Heart Failure. *Tex. Heart Inst. J.* **2016**, *43*, 297–304. [[CrossRef](#)]
110. Wood, N.; Johnson, R.B. The relationship between tomato intake and congestive heart failure risk in periodontitis subjects. *J. Clin. Periodontol.* **2004**, *31*, 574–580. [[CrossRef](#)]
111. Schulze-Späte, U.; Mizani, I.; Salaverry, K.R.; Chang, J.; Wu, C.; Jones, M.; Kennel, P.J.; Brunjes, D.L.; Choo, T.H.; Kato, T.S.; et al. Periodontitis and bone metabolism in patients with advanced heart failure and after heart transplantation. *ESC Heart Fail.* **2017**, *4*, 169–177. [[CrossRef](#)]

112. Carinci, F.; Martinelli, M.; Contaldo, M.; Santoro, R.; Pezzetti, F.; Lauritano, D.; Candotto, V.; Mucchi, D.; Palmieri, A.; Tagliabue, A.; et al. Focus on periodontal disease and development of endocarditis. *J. Biol. Regul. Homeost. Agents* **2018**, *32*, 143–147.
113. Oliveira, F.A.; Forte, C.P.; Silva, P.G.; Lopes, C.B.; Montenegro, R.C.; Santos, Â.K.; Sobrinho, C.R.; Mota, M.R.; Sousa, F.B.; Alves, A.P. Molecular Analysis of Oral Bacteria in Heart Valve of Patients With Cardiovascular Disease by Real-Time Polymerase Chain Reaction. *Medicine (Baltimore)* **2015**, *94*, e2067. [[CrossRef](#)]
114. Sekinishi, A.; Suzuki, J.; Aoyama, N.; Ogawa, M.; Watanabe, R.; Kobayashi, N.; Hanatani, T.; Ashigaki, N.; Hirata, Y.; Nagai, R.; et al. Periodontal pathogen *Aggregatibacter actinomycetemcomitans* deteriorates pressure overload-induced myocardial hypertrophy in mice. *Int. Heart J.* **2012**, *53*, 324–330. [[CrossRef](#)]
115. Kozarov, E.V.; Dorn, B.R.; Shelburne, C.E.; Dunn, W.A., Jr.; Progulske-Fox, A. Human atherosclerotic plaque contains viable invasive *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, e17–e18. [[CrossRef](#)] [[PubMed](#)]
116. Lanter, B.B.; Sauer, K.; Davies, D.G. Bacteria present in carotid arterial plaques are found as biofilm deposits which may contribute to enhanced risk of plaque rupture. *MBio* **2014**, *5*, e01206–e01214. [[CrossRef](#)]
117. Lanter, B.B.; Davies, D.G. *Propionibacterium acnes* Recovered from Atherosclerotic Human Carotid Arteries Undergoes Biofilm Dispersion and Releases Lipolytic and Proteolytic Enzymes in Response to Norepinephrine Challenge In Vitro. *Infect. Immun.* **2015**, *83*, 3960–3971. [[CrossRef](#)] [[PubMed](#)]
118. Snow, D.E.; Everett, J.; Mayer, G.; Cox, S.B.; Miller, B.; Rumbaugh, K.; Wolcott, R.A.; Wolcott, R.D. The presence of biofilm structures in atherosclerotic plaques of arteries from legs amputated as a complication of diabetic foot ulcers. *J. Wound Care* **2016**, *25*, S16–S22. [[CrossRef](#)] [[PubMed](#)]
119. Li, X.; Kolltveit, K.M.; Tronstad, L.; Olsen, I. Systemic Diseases Caused by Oral Infection. *Clin. Microbiol. Rev.* **2000**, *13*, 547–558. [[CrossRef](#)] [[PubMed](#)]
120. Gomes-Filho, I.S.; Freitas Coelho, J.M.; da Cruz, S.S.; Passos, J.S.; Teixeirade Freitas, C.O.; Aragao Farias, N.S.; Amorim da Silva, R.; Silva Pereira, M.N.; Lima, T.L.; Barreto, M.L. Chronic periodontitis and C-reactive protein levels. *J. Periodontol.* **2011**, *82*, 969–978. [[CrossRef](#)] [[PubMed](#)]
121. Ridker, P.M. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: Moving an inflammatory hypothesis toward consensus. *J. Am. Coll. Cardiol.* **2007**, *49*, 2129–2138. [[CrossRef](#)]
122. Kleindienst, R.; Xu, Q.; Willeit, J.; Waldenberger, F.R.; Weimann, S.; Wick, G. Immunology of atherosclerosis: Demonstration of heat shock protein 60 expression and T lymphocytes bearing alpha/beta or gamma/delta receptor in human atherosclerotic lesions. *Am. J. Pathol.* **1993**, *142*, 1927–1937. [[PubMed](#)]
123. Loesche, W.J.; Lopatin, D.E. Interactions between periodontal disease, medical diseases and immunity in the older individual. *Periodontology 2000* **1998**, *16*, 80–105. [[CrossRef](#)] [[PubMed](#)]
124. Chen, Z.Y.; Chiang, C.H.; Huang, C.C.; Chung, C.M.; Chan, W.L.; Huang, P.H.; Lin, S.J.; Chen, J.W.; Leu, H.B. The association of tooth scaling and decreased cardiovascular disease: A nationwide population-based study. *Am. J. Med.* **2012**, *125*, 568–575. [[CrossRef](#)]
125. Chou, S.H.; Tung, Y.C.; Lin, Y.S.; Wu, L.S.; Lin, C.P.; Liou, E.J.; Chang, C.J.; Kung, S.; Chu, P.H. Major Adverse Cardiovascular Events in Treated Periodontitis: A Population-Based Follow-Up Study from Taiwan. *PLoS ONE* **2015**, *10*, e0130807. [[CrossRef](#)] [[PubMed](#)]

