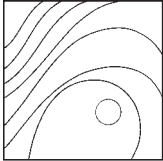


# The Link Between Periodontitis/Peri-implantitis and Cardiovascular Disease: A Systematic Literature Review



Stuart J. Froum, DDS<sup>1</sup>/Parnward Hengjeerajaras, DDS<sup>2</sup>  
Kuan-You Liu, DDS<sup>3</sup>/Panpicha Maketone, DDS<sup>4</sup>  
Viraj Patel, BDS (Hons)<sup>2</sup>  
Ye Shi, DDS, MS<sup>2</sup>

*A link between periodontitis and cardiovascular disease has been reported in the literature. For this systematic review, the keywords "cardiovascular disease" (CVD) were combined with "periodontitis" and "peri-implantitis" and were used to search for literature published on MEDLINE and PubMed between 1990 and 2020. Hand searching was also performed. A total of 206 articles were identified, 51 of which were reviewed. A link between periodontal disease and CVD can be explained by both the infection and inflammatory pathways. Interventional studies on the treatment of periodontal disease related to CVD have shown conflicting results. Therefore, based on published studies, CVD should presently be considered a comorbidity of periodontitis (with an association but no direct cause and effect documented). The association of CVD with peri-implantitis has too few studies to draw any conclusions. More studies are necessary before any conclusions can be made between CVD and periodontitis and CVD and peri-implantitis regarding possible links and the extent of association. Int J Periodontics Restorative Dent 2020;40:e229–e233. doi: 10.11607/prd.4591*

Periodontitis has been defined as an inflammatory disease of the supporting tissues of the teeth that is characterized by "an extension of inflammation from the gingiva into the adjacent bone with lysis of the gingival fibers, formation of periodontal pockets, and resorption of bone."<sup>1</sup> The 1993 European Workshop on Periodontology determined that the classification of periodontitis should be grouped into two major headings: adult and early onset periodontitis.<sup>2</sup> For years, periodontitis was recognized as a localized disease, the etiology of which was demonstrated as bacterial plaque (biofilm) residing in the oral cavity.<sup>3–5</sup> At a recent consensus conference, a new classification of periodontitis has been proposed that includes designations for disease type and speed of progression.<sup>6</sup> However, much of the literature mentioned in the present review was published prior to the new classification and thus refer to the original periodontitis definition.<sup>1</sup>

Over the last several decades, many studies have established an association between cardiovascular disease (CVD) and periodontitis. According to a number of authors, periodontitis has been demonstrated as more prevalent in patients with CVDs; conversely, many patients with periodontitis have been shown to be more likely to develop

<sup>1</sup>Ashman Department of Periodontology and Implant Dentistry, New York University College of Dentistry, New York, New York, USA; Private practice, New York, New York, USA.

<sup>2</sup>Ashman Department of Periodontology and Implant Dentistry, New York University College of Dentistry, New York, New York, USA.

<sup>3</sup>Private practice, Taiwan, China.

<sup>4</sup>Ashman Department of Periodontology and Implant Dentistry, New York University College of Dentistry, New York, New York, USA; Eastman Institute for Oral Health, University of Rochester, Rochester, New York, USA.

Correspondence to: Dr Stuart J. Froum, 17 West 54th Street, Suite 1c/d, New York, NY 10954, USA. Email: dr.froum@verizon.net

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CVDs.<sup>7</sup> Lastly, treatment of periodontitis has in some cases reduced the incidence/damage to the body caused by CVD.<sup>8</sup>

Peri-implantitis is a pathologic condition of the tissues surrounding dental implants, characterized by inflammation in the mucosa that leads to subsequent loss of supportive bone beyond physiologic modeling/remodeling.<sup>9</sup> Periodontitis has been documented as a risk factor for peri-implantitis. Both are inflammatory diseases that affect the soft tissue and supporting bone around teeth and implants.<sup>10</sup> Because the use of dental implants to restore missing or soon-to-be-missing teeth has increased, the prevalence of peri-implantitis has also increased. According to the literature, the prevalence of peri-implantitis can vary from 6% to 54%.<sup>11,12</sup> The etiology and clinical features of this disease are similar to periodontal disease: ie, bacterial biofilm forming on the implant surface, which interacts with the surrounding host tissue, leading to destructive changes in supporting bone.<sup>13–15</sup>

The first aim of the current paper was to review the literature to determine whether an association exists between CVD and periodontitis and then to evaluate whether intervention in the treatment of periodontitis had a positive effect on CVD status.<sup>3</sup>

The second aim was to determine if peri-implantitis, according to the literature review, showed any association with CVD.

## Materials and Methods

A MEDLINE, PubMed, and hand searches were conducted of the literature published between 1990 and 2020. Using the words “cardiovascular disease” along and combined with “periodontitis,” “periodontal disease,” and “peri-implantitis,” a total of 206 articles were reviewed, 51 of which were selected for the present review based on the pertinence to the manuscript topic. Disagreements were decided by consensus of the authors’ (P.M., P.H., and S.F.) opinions, relevance to the topic, and aims of the review.

CVD has been defined as a group of disorders of the heart and blood vessels including hypertension, coronary heart disease, cerebrovascular disease, peripheral vascular disease, heart failure, rheumatic heart disease, congenital heart disease, and cardiomyopathy.<sup>16</sup>

According to a survey from the American Heart Association, CVD is listed as the most common underlying cause of death and accounts for nearly 801,000 deaths in the United States per year, which is approximately 1 of every 3 deaths in the US. About 92.1 million American adults (47.7% of women and 46.0% of men) are living with different forms of CVD or the after-effects of stroke.<sup>17</sup> Chronic inflammation clearly plays a crucial role in both the initiation and progression of the chronic diseases prevailing today, including CVD.<sup>18</sup> Among all the chronic inflammatory disease in adults, periodontitis is one of the highest in prevalence. According to Eke et al, “an estimated 42% of dentate US adults 30 years

or older had periodontitis, with 7.8% having severe periodontitis.”<sup>19</sup> Further, Eke et al found that “as a result of its chronic and cumulative nature, periodontitis is more common in older adults, with two-thirds (68%) of persons  $\geq 65$  years of age being affected with chronic periodontitis.”<sup>20</sup>

## Association of CVD and Periodontitis

### *Link to Periodontitis*

A number of studies reported that patients with periodontitis had a significantly increased risk of developing CVD.<sup>21–23</sup> In addition, several papers reported that periodontitis is associated with many different forms of CVD, such as hypertension, ischemic stroke, atherosclerosis, hemorrhagic stroke, and coronary heart disease.<sup>24–28</sup> In one meta-analysis, the increase in the relative risk of coronary heart disease among subjects with periodontitis compared to healthy subjects was 1.15 (95% confidence interval: 1.06 to 1.25).<sup>29</sup> Another study has shown a 25% increased risk of developing heart disease in periodontitis patients compared to healthy subjects, providing further support to the statement that “heart disease is the most commonly found systemic condition in patients with periodontal disease.”<sup>30</sup> Moreover, studies by Beck et al, Joshipura et al, and DeStefano et al showed that infection and inflammation caused by periodontal disease increased the risk of coronary heart disease.<sup>23,31,32</sup>

### Possible Mechanism

Periodontitis and CVD have the same causative pathogens. A cross-sectional study in 2007 reported a relationship between periodontopathic anaerobic bacteria and atherosclerosis.<sup>33</sup> It is thought these pathogens increase platelet aggregation thereby increasing the possibility of inducing thromboembolic events.<sup>30</sup> Other studies have reported that the bacterial species found in subgingival plaques were also found in the atherosclerotic plaques. The bacterial species most commonly found were *Porphyromonas gingivalis*, followed by *Aggregatibacter actinomycetemcomitans* and *Tannerella forsythia*.<sup>34,35</sup> A second possible mechanism is through systemic inflammation and increased circulating cytokines and inflammatory mediators (especially C-reactive protein [CRP]). Inflammation increases the concentration of circulating cytokines, which in turn damages the vascular endothelium and ultimately results in atherosclerosis. Elevated plasma CRP levels are considered a key marker of atherosclerosis, and its increased level constitutes a significant risk predictor for the presence of CVD.<sup>36,37</sup> A study by Shojaaee noted an increased level of salivary CRP in patients with periodontitis compared to healthy subjects.<sup>38</sup> Furthermore, a number of studies reported raised CRP levels in periodontitis patients.<sup>36,37</sup> This can also be linked to the bacterial flora in periodontitis patients (*P. gingivalis*), which have been associated with increased CRP levels, stimulation of CD36 proteins, and activation of

oxidized low-density lipoproteins, leading to the activation of pathways that generate proinflammatory molecules, which may also lead to atherosclerosis.<sup>37,39</sup> Despite the similarities in bacterial pathogens and the inflammatory cascade in CVD and periodontitis, further research is needed to understand exactly how periodontitis may influence CVD.

### Intervention Studies

Numerous studies have reported that levels of proinflammatory markers are increased in patients with CVD. The most common markers of systemic inflammation are serum interleukin-6 and CRP.<sup>40</sup> One study reported that subgingival debridement reduced the risk of aggregated platelet activation<sup>41</sup> and showed decreased levels of transforming growth factor beta (TGF- $\beta$ ) in the gingival crevicular fluid after 7 days of treatment.<sup>42</sup> Another study reported that periodontal treatment is effective in reducing CRP and TGF- $\beta$  levels.<sup>43</sup> Therefore, treatment of periodontitis may potentially diminish CVD in patients with periodontitis.

### Negative Studies

One literature review concluded that there is insufficient evidence to support or refute whether periodontal therapy can prevent the recurrence of CVD in the long term in patients with chronic periodontitis.<sup>44</sup>

A statement from the American Heart Association reported that "Observational studies to date sup-

port an association between periodontal disease and atherosclerotic vascular disease (ASVD) independent of known confounders. They do not, however, support a causative relationship." Additionally, they reported that "although periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction in short-term studies, there is no evidence that they prevent ASVD or modify its outcomes."<sup>42</sup>

### Association of CVD and Peri-implantitis

#### Link to Peri-implantitis

A cross-sectional study published by Renvert et al found an odds ratio (OR) of 8.7 for the association of CVD with peri-implantitis, which exceeded the OR for an association with periodontitis (OR of 4.5).<sup>45</sup> A systemic review by Turri et al reported that smoking, poorly controlled type 2 diabetes and cardiovascular diseases were considered risk factors associated with peri-implantitis.<sup>46</sup> An article by Saaby et al reported that systemic disease was present in 44% of the patients who were referred for treatment of peri-implantitis, with CVD present in 26% of the patients treated.<sup>47</sup> Froum et al treated 100 patients with 170 peri-implantitis-affected implants and reported 48 of 100 patients had a history of hypertension. The authors concluded that there has been little or no mention of hypertension (controlled) as a risk factor for peri-implantitis and that this risk factor should be noted and studied.<sup>48</sup>

### Possible Mechanism

The literature has reported a similar bacterial flora associated with periodontitis and peri-implantitis.<sup>49</sup> Therefore, as suggested above in the possible mechanisms for the association of periodontitis and CVD, the similarities in bacterial flora and the increase in systemic inflammation could possibly link CVD and peri-implantitis. However, due to the limited literature on the relationship between CVD and peri-implantitis, a possible mechanism is still not fully understood.

### Intervention Studies

No interventional studies have been published regarding the effect of peri-implantitis treatment on CVD.

### Negative Studies

Regarding peri-implantitis, some authors reported no association between systemic condition and peri-implantitis. Koldslund et al evaluated CVD but failed to observe an association with peri-implantitis.<sup>50</sup> Roos-Jansåker et al combined different systemic diseases (diabetes, osteoporosis, and coronary heart disease) into one parameter and found no elevated risk for peri-implantitis.<sup>51</sup>

### Conclusions

CVD has been shown to have an association with periodontal disease. Systemic inflammation and

endothelial dysfunction have been shown to be related to CVD and periodontal disease, and treatment of the latter may decrease the incidence of CVD. However, interventional studies on the treatment of periodontal disease have shown conflicting results. Therefore, based on the published studies, CVD should at least be considered a comorbidity of periodontitis without a documented cause-and-effect relationship. More studies are needed to determine if periodontal disease can influence the prevalence or severity of CVD. Studies involving larger, better-controlled, and more socially homogenous populations are necessary to correlate a definitive association between CVD and periodontal disease. Moreover, since periodontitis has been identified as a possible risk factor for CVD in several studies, additional interventional studies are needed to determine if periodontal treatment can decrease the risk of CVD.

The association of CVD with peri-implantitis has too few studies to draw any conclusions but should be considered, as inflammation is a component of both diseases. Due to the heterogeneity of populations in present studies, looking at CVD and peri-implantitis, a meta-analysis has not been performed to date. More studies are necessary before any conclusions can be made about any possible links between CVD and peri-implantitis.

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