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Is the Association between Periodontitis and Cardiovascular Diseases Causal?

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Abstract:

Background
Periodontitis (PD) and cardiovascular diseases (CVDs) are regarded as chronic inflammatory disorders and are among the most prevalent non-communicable diseases in the world. Observational studies have demonstrated a consistent relationship between PD and CVDs. Indeed, patients with PD have a moderately higher risk of CVDs, including stroke and myocardial infarction (MI). Several possible mechanisms, which include bacterial dissemination, systemic inflammation and microbiome changes, have been proposed. This review aims to appraise the existing evidence on the potential benefits of improving periodontal health in terms of future cardiovascular risk.

Method
This is a narrative review on the relationship between PD and CVDs. A literature review of randomized clinical trials and observational studies in the English language was done by one investigator (EHK) using MEDLINE OVID and Cochrane Oral Health Group's Trial Register database up to March 2018. It was limited to the terms 'cardiovascular diseases,' 'myocardial infarction,' 'coronary heart disease,' 'periodontal,' 'periodontitis,' 'treatment,' 'clinical trial,' 'systematic review' and 'meta-analysis.' The search identified 24 articles in the Cochrane database and 84 articles in MEDLINE. References cited in the reviewed studies were assessed and included in the study if relevant.

Results
The search reaffirmed a relationship between the two diseases, with an average 15% higher risk of CVD in patients with PD. Nevertheless, no evidence was found to suggest that improved periodontal health affects CVD hard outcomes, such as stroke or MI. On the other hand, improving periodontal health ameliorates subclinical atherosclerosis, endothelial function and biomarkers of systemic inflammation.

Introduction

Cardiovascular diseases (CVDs) refer to a category of non-communicable conditions such as coronary heart disease, stroke, congestive heart failure, and peripheral artery disease. The classical risk factors for CVDs include male gender, an older age, having a family history of CVDs, smoking, diabetes mellitus, obesity, hypertension, hyperlipidemia and a sedentary lifestyle.[1] These established risk factors are believed to contribute to 70–90% of the incidence of coronary heart disease.

Periodontitis, which has been identified as the sixth most common non-communicable disease by the World Health Organization, is a chronic inflammatory disease.[2] Periodontitis initially manifests as local gingival inflammation and progresses into soft tissue attachment and eventual tooth loss if left untreated.[3] Periodontitis is not confined to the oral cavity, as it causes systemic inflammation as part of a chronic host response.[4]

Biological plausibility: an explanation of the proposed mechanisms of association

A number of plausible biological mechanistic models support the relationship between PD and CVDs.[5–7] The first model of association is based on the excessive inflammatory response triggered by the gingival lesions.[7] There is no doubt that inflamed periodontal pockets are a great reservoir of cytokines and other inflammatory mediators.[8] Patients with periodontitis exhibit higher local and systemic levels of inflammatory mediators, such as IL-1, IL-6, CRP, and TNF-α when compared to controls.[9] This elevation could be the result of a "spillover" of local inflammatory mediators into the systemic circulation. If this hypothesis is correct, these mediators might negatively affect distant tissues/organs. For instance, the liver is the most common target of this local inflammatory burden, which turns into a systemic acute-phase response and could impact other distant organs or inflammatory disorders. The inner blood vessel layer (endothelium) is also affected by PD, and an upregulation of adhesion molecules and cytokines could contribute to the development and progression of vascular dysfunction and atherogenesis.[10] However, there is little clinical evidence to back this hypothesis, and further research is required.[11]

The alternative mechanism suggested is bacterial dissemination via the ulcerated periodontal pocket and invasion into the bloodstream.[6] The endothelium and immune cells are the main cells involved in the subsequent inflammatory response.[6,9] Bacteria can evade the endothelial barrier and stimulate peri-vascular local inflammation. The detection of bacterial DNA in carotid arteries specimens and also other remote sites have proven this remote movement of bacteria.[12] Bacteria can directly impair the function of blood cells, such as the platelets, by causing hypercoagulability[13] or penetrating the host's immune cells, such as dendritic cells, and being transported to remote areas, stimulating local inflammation.[14] The bacterial burden triggers an inflammatory response which ultimately targets the endothelial cell and might contribute to atheroma development, maturation and exacerbation.[15]

Another plausible mechanism, which has been proposed more recently, suggests that the link between PD and CVDs lies in the association between systemic inflammation and the microbiota in the gastrointestinal tract.[5] This mechanism is supported by animal studies, in which Porphyromonas gingivalis was found to be related to the alteration of the composition of gastrointestinal microbiota and the indirect induction of systemic inflammation in mice.[16] Periodontal pathogens originating from oral districts have been implicated (via ingestion) into modification of gastrointestinal microbiota.[16] Additionally, the spreading of bacterial by-products (i.e., secreted by bacterial metabolism) into the blood circulation has been proposed as an additional mechanism that impairs endothelial and vascular functions.[5]

Epidemiological evidence: summary of the most relevant result

The association between poor oral health and CVDs was firstly demonstrated in a seminal case-control study led by a Finnish cardiologist who compared the oral health of patients with MI with that of healthy controls.[17] The main result of the study was that poorer oral/periodontal health was noted among patients with MI.[17] In 2013, the American Academy of Periodontology and the European Federation of Periodontology confirmed an independent association between periodontitis and atherosclerotic disease.[15]

Recently published observational evidence has further strengthened the link between PD and CVD. A large case-control study involving 800 MI patients and 800 controls investigated the association between MI and periodontal health. The PAROKRANK investigators concluded that patients with periodontitis presented with a 30% increased risk of MI, and this was independent of other common CVD risk factors such as age, gender, smoking, and body mass index.[18]

A recent large-scale cohort study (1400 men) investigating the relationship of periodontitis with death from all causes in West European men ranging from 60 to 70 years old reported that those participants presenting with severe periodontal attachment loss were two times more likely to die during a period of nine years.[19] Additionally, the study also demonstrated that patients with periodontitis were 15% more likely to develop CVDs in the future.[19]

A cohort study was recently completed and it concluded that oral health is equally linked to three different CVDs: MI, stroke, and heart failure (HF).[20] Nearly 9000 participants were followed up for 15.8 years. The study reported that the number of teeth of the participants was significantly associated with

the incidence of MI and HF, but not stroke.

Apart from the extent of periodontal attachment loss, the measurement of serum antibody titer towards *Porphyromonas gingivalis* was proposed as being related to the history of MI and PD in a recent case-control study. [21] Ninety-seven patients with a history of MI and 113 controls with high risk factors but no history of coronary heart disease were included in the study. The test group and the control group had similar distributions of age, gender and location of dwelling. Periodontal health was examined using the Community Periodontal Index (CPI) and by examining clinical attachment loss (CAL), bleeding on probing (BOP) and probing pocket depth (PPD). This study reported a link between a history of MI and clinical measurement of chronic periodontitis such as BOP, CPI code and CAL. Additionally, they also found that patients with moderate antibody titer levels against *P. gingivalis* were also associated with three times higher odds of previous MI.

Proposed benefits of periodontal health/treatment on CVD outcomes

Currently, there is scarce evidence suggesting that periodontal treatment prevents CVDs. To the best of our knowledge, only two clinical studies have investigated the influence of periodontal treatment on the prevention of CVD events, and no positive outcomes were reported. [22,23] Insufficient evidence has been reported to support the effects of periodontal intervention on CVD events. However, a positive outcome was observed in the reduction of serum C-reactive protein (CRP) levels and the improvement of endothelial function. Serum CRP levels and endothelial functions are both predictors of future CVD events. However, the validity of these variables was questioned. It was contended that CRP levels might simply reflect the overall effect of some undiscovered CVD risk factors, [24] whilst endothelial dysfunction was disputed due to the possibility of being biased by the methodological and environmental components. Therefore, other parameters, such as the intima-media thickness of the common carotid artery (c-IMT) and flow-mediated dilatation (FMD), were applied to predict the future risk of CVD events. [25] Intima-media thickness of the common carotid artery (c-IMT) reflects subclinical atherosclerosis, while flow-mediated dilatation (FMD) shows endothelial dysfunction, which occurs at the early stages of atherogenesis. [26] Impaired endothelial function (stiffer arteries) or a larger thickness of c-IMT contributes to a higher risk of future CVD events.

One of the largest randomized trials was done by Tonetti et al. to investigate the association between periodontal therapy and endothelial function. One hundred and twenty patients suffering from generalized severe periodontitis with no other co-morbidities were recruited. CVD-related parameters such as endothelial function, which was reflected by the diameter of the brachial artery during blood flow (flow-mediated dilation), inflammatory biomarkers, markers of coagulation and endothelial activation were collected before the experiment and up to 6 months following the treatment. [27] The study showed that rapid-onset, temporary, systemic inflammation and endothelial dysfunction were observed following thorough periodontal treatment. Nevertheless, periodontal therapy, which consists of non-surgical treatment and local antibiotics, improved the endothelial function by at least 1% at 6 months after the completion of therapy. [27]

Two more recent studies (a cohort study by Piconi et al. and a randomized trial on 168 Australians) reported a significant change in c-IMT following periodontal therapy. [28,29] In particular, the randomized study reported a 0.026 mm increase in c-IMT in the test group only. Lack of appropriate controls and reliable vascular measurements limit the validity of these results.

Forearm blood-flow changes following periodontal treatment have been also investigated as a proxy measure of endothelial function. [30,31] In two randomized clinical trials, the responses of forearm blood flow to acetylcholine and sodium nitroprusside were compared before and after periodontal therapy. The response of forearm blood flow before and after the treatment was also measured following the use of NG-monomethyl-L-arginine, an NO synthase inhibitor. In the first study, the endothelial function was investigated in periodontitis patients without cardiovascular risk factors and in periodontitis patients with hypertension. [30,31] Four different groups of patients were recruited: patients with PD but no other cardiovascular risk factors, healthy individuals without cardiovascular risk factors, hypertensive patients with PD, and hypertensive patients without PD. The studies revealed that the responses of forearm blood flow to acetylcholine in both healthy and hypertensive patients with periodontitis were significantly smaller than in the control

group. However, the measurements were close to each other following the use of NG-monomethyl-L-arginine. These results proposed that, by reducing the NO bioavailability and promoting systemic inflammation, periodontitis leads to endothelial dysfunction in both sets of patients independently of cardiovascular risk factors and hypertension. The second study focused on the endothelial function in patients with coronary artery disease (CAD) who also had PD. [30] The design and results of this study were similar to the previous study, despite the different population recruited.

A systematic review appraising the evidence linking c-IMT, FMD and PD confirmed, firstly, that patients with PD have a larger c-IMT and reduced FMD, [32] and secondly, that periodontal treatment improves endothelial function by 6.64%, on average, when compared to controls. The authors proposed that the improvement on endothelial function following periodontal therapy could result in a reduction of CVDs, including stroke and MI. [32] Furthermore, the only randomized clinical trial available for the intimal medial layer of the carotid artery (c-IMT) reported that periodontal treatment reduced the c-IMT by 0.026 mm ([95% CI, -0.048 to -0.003] mm; P=0.03). [33] In order to interpret these results, we should consider the data from an observational study using c-IMT as a predictor of death/complications. In that study, a 0.03 mm annual increase in c-IMT was linked with a twofold risk of non-fatal MI.[34]

The impact of periodontal therapy on novel CVD risk factors, including a variety of serum biomarkers, was also examined [19]. The randomized clinical trial carried out by D'Aiuto et al. studied the effects of periodontal therapy on serum inflammatory biomarkers and cholesterol levels among patients with generalized severe chronic periodontitis. [35,36] They concluded that non-surgical debridement resulted both in an acute increase of CRP and interleukin (IL)-6 [35] over the first week following treatment, while two months following therapy, there was a significant decrease in both CRP and IL-6. [36] Whilst substantial evidence has been produced regarding the positive effects of periodontal therapy on CRP and IL-6, the same conclusion cannot be drawn for the effects of periodontal therapy on leucocyte counts, lipid fraction, fibrinogen, serum amyloid A, TNF-α and other interleukins. [37]

Conclusion

In conclusion, a plethora of studies demonstrate a consistent relationship between PD and CVDs, and how PD is an independent risk factor for CVDs. Additionally, positive outcomes of periodontal treatment on surrogate measures of cardiovascular health are available.

Despite lacking evidence of a robust effect of improved periodontal health on MI and strokes, all health professionals (medical and dental) should work together to promote oral health with the aim of improving patients overall quality life and raising awareness of both disorders.

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