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Review Article

Periodontitis and coronary artery disease: a questioned association between periodontal and vascular plaques

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Abstract: Periodontitis is a bacterially-induced, localized chronic inflammatory disease destroying both the connective tissue and the supporting bone of the teeth. In the general population, severe forms of the disease demonstrate a prevalence of almost 5%, whereas initial epidemiological evidence suggests an association between periodontitis and coronary artery disease (CAD). Both the infectious nature of periodontitis and the yet etiologically unconfirmed infectious hypothesis of CAD, question their potential association. Ephemeral bacteremia, systemic inflammation and immune-pathological reactions constitute a triad of mechanisms supporting a cross-talk between periodontal and vascular damage. To which extent each of these periodontitis-mediated components contribute to vascular damage still remains uncertain. More than twenty years from the initial epidemiological association, the positive weight of evidence remains still alive but rather debated, because of both the presence of many uncontrolled confounding factors and the different assessment of periodontal disease. From the clinical point of view, advising periodontal prevention or treatment targeting on the prevention of CAD it is unjustified. By contrast, oral hygiene including periodontal health might contribute to the overall well-being and healthy lifestyle and hence as might at least partially contribute to cardiovascular prevention.

Keywords: Periodontitis, periodontal disease, coronary artery disease, prevention, bacteremia, atherosclerosis

Infections and coronary artery disease

Established risk factors such as arterial hypertension, smoking, hyperlipidaemia, obesity and diabetes mellitus may explain at least partially the development of coronary artery disease (CAD) [1]. However, many cases of CAD develop in the absence of traditional cardiovascular risk factors and among these lines additional contributing factors such as genetic predisposition, have been proposed to culminate the partially unexplained etiology of cardiovascular diseases [2]. Beyond the genetic predisposition which resides in the setting of the not-modifiable risk factors, in the recent years, researchers called attention on an old theory promoting atherogenesis, that is the duo of inflammation and infection [3].

The coexistence of infections with CAD has been shown in both *ex vivo* and *in vivo* studies [4]. *Ex vivo* studies demonstrated the presence of specific infectious agent-related proteins or bacterial DNA in vascular tissue specimens of patients with carotid and coronary atherosclerosis [5, 6]. *In vivo* evidence becomes from experimental models - almost one century ago – where infections were capable to promote histopathologically recognized areromatosous arteritis [7, 8]. Another line of evidence becomes from serological studies suggesting increased antibody titers for specific infectious agents in patients with overt cardiovascular disease. During the last two decades of the previous century, three types of infectious agents have been extensively studied for their relationship with CAD: cytomegalovirus, chlamydia pneumoniae and helicobacter pylori [4]. Although experimental evidence suggested the potential infectious hypothesis of atherogenesis, subsequent randomized controlled trials implementing antibiotics refused the infectious etiological hypothesis (i.e. that the eradication of the infection would be accompanied by reduced incidence of vascular events) [9-13]. The latter failing association was not enough for researchers to reject the

ongoing investigation for the association between CAD and focal bacterial-mediated chronic inflammatory disease taking place on the periodontal tissue, namely periodontitis [4, 14, 15].

Periodontal disease

Periodontal disease is defined by the anatomical destruction of the tissues supporting the tooth that occurs following the disease physical history. The progression of the disease is low and the severity is measured on the basis of the amount of periodontal tissue destruction. If the disease progress without therapeutic interventions the final outcome is the loss of the teeth. Another way to define the magnitude of the disease is to measure the focal infection load or even its systemic inflammatory or immunological repercussion. Furthermore, the focal progression of periodontal disease correlates to inflammatory biomarkers such as pro-inflammatory cytokines and serum antibody titers for pathogen periodontal bacteria.

However, given the assay variability of all these bloodstream inflammatory and immunological mediators, focal measures of periodontal disease seem more accurate in order to define disease severity. Eventually, combination of bloodstream mediators with focal measures of the disease might be more informative and studies dealing with both conditions may provide a more integrated view of the disease process. Indeed, in a hypertensive substrate we demonstrated that the magnitude of periodontal tissue severity accompanied by increased levels of C reactive protein resulted in more pronounced albuminuria as compared with lower levels of C reactive protein [16].

Focal Measures of periodontal disease: different modalities to assess the exposure variable

Etiologic bacteria: The identification of etiologic bacteria in periodontal pockets such as the *Porphyromonas gingivalis* could provide evidence for periodontal disease. However, the latter does not represent the obvious marker to define enhanced periodontal severity since it could be found in patients with less severe disease. The amount of the infective load is generally estimated through bacterial DNA amplification with nested-PCR, a procedure used only for investigational and not for clinical-oriented purposes.

Periodontal disease indexes: Apart from full examination of the intra-oral tissues, gingival and periodontal probing test is always performed. All teeth surfaces are probed for periodontal disease assessment with special probes. Probing depth and clinical attachment level are recorded for all of the teeth at each of six locations (i.e. buccal, lingual, mesiobuccal, mesiolingual, distolingual and distobuccal). Thereafter, the following parameters of periodontal disease are measured: mean clinical loss of attachment (i.e. mean distance among the examined sites, between the cementoenamel junction to base of pocket or crevice), maximum probe depth (i.e. maximum measured distance between the free gingival bleeding margins to the base of pocket or crevice) and gingival bleeding index (i.e. ratio between the number of periodontal bleeding sites by probing to the total examined periodontal sites). All these indexes are important to clinically evaluate the progression of periodontal disease.

Bone loss: dental radiography scans are performed in order to measure the quantity of bone loss supporting the diseased teeth. Bone loss constitutes an irreversible consequence of periodontal disease, but especially in women after menopause might be a consequence of ongoing osteoporosis and not of periodontal disease progression alone.

Teeth loss: measuring the number of the remaining teeth in a patient with periodontal disease might be the more objective measure for the definition of periodontal disease. However, other than reflecting the final stage of periodontitis, measurement of the remaining teeth number might also reflect the physical extinction of the disease corresponding to the edentulous condition.

Community periodontal index for treatment needs (CPITN): that index was developed jointly by the International Dental Federation and World Health Association in 1983: it is easy to use, permits rapid examination of large population groups, and aims to evaluate periodontal condition and treatment needs. However, CPITN may overestimate treatment needs given that it is based on a hierarchical concept of periodontal disease progression. Additionally, CPITN scoring does not account for tooth mobility and loss of attachment, both important parameters for the completeness of periodontal disease

Table 1. Community Periodontal Index for Treatment Needs (CPITN) and total dental index (TDI) components for assessing oral health

CPITN		TDI	
Score	Condition	Type of disease	Score
	No bleeding	CARIES	
0	No calculus	No carious lesion	0
	No pathological pocket	1-3 carious lesions	1
		4-7 carious lesions	2
		≥8 carious lesions	3
	Bleeding on probing gingival margin	PERIODONTITIS	
1	No calculus	None	0
	No pathological pocket	Gingival pocket 4-5mm	1
		Gingival pocket ≥6mm	2
		Macroscopic pus	3
	Presence of calculus (sub or supra gingival)	PERIAPICAL LESIONS	
2	with or without bleeding	None	0
	No pathological pocket	1 or vertical bone pocket or both	1
		2	2
		≥3	3
3	Pathological pocket of 4-5 mm with or without	PERICORONARITIS	
	bleeding and calculus	No	0
		Yes	1
4	Pathological pocket of 6 mm or more		
	with or without bleeding and calculus		

evaluation. Another integrated index to assess oral health is the total dental index which includes the assessment of periodontal deterioration (**Table 1**).

Self-reported periodontal disease: based on different questionnaires [16-18].

Epidemiological evidence for the association between periodontal and coronary artery disease

In a systematic review [19] examining five prospective studies with approximately 90,000 patients with periodontitis the relative risk for CAD was 14% in almost ten years. In the same metanalysis and accounting only for case-control studies the relative risk for prevalent periodontal disease was 120% for the cases compared to controls and finally in cross-sectional studies that risk was higher in the former group by 60% compared to the latter. Although prospective studies demonstrated only a fair positive association, these studies were not *a priori* designed to address the hypothesis of the association between periodontal disease and CAD, and finally periodontitis in most of them was self-reported and not objectively quantified (**Table 2**).

The first study that evaluated the association between CAD and periodontal damage was the study by Mattilla et al. [20] Researchers studied males admitted in the hospital for myocardial infarction and compared their periodontal status with healthy controls from the same urban population. Those with an acute event demonstrated a more deteriorated periodontal status with respect to their matched controls. Interestingly, Mattilla et al implemented a more integrated approach to define oral hygiene including the combined evaluation of caries, periodontitis, periapical lesions and pericoronitis (**Table 1**). Additionally, low levels of high-density lipoprotein protein and smoking status (current and former) constituted significant determinants of CAD, whereas other factors such as low socio-economic status, hypertension, diabetes, and age failed to correlate with the same outcome. Since, both periodontal disease and CAD are correlated with all of these latter risk factors, statistical adjustment for all of these confounders might be an eternal unfulfilled target to address. Another issue that might have contributed to the association between CAD and oral hygiene is that patients were examined just after the acute coronary event, and the inverse relationship (that is, acute myocardial infarction determined adversely oral hygiene) could not be

Table 2. Shared risk factors and methodological issues modulating the association between periodontitis and CAD

Shared Risk Factors	Methodological issues
Smoking status	Different definitions of periodontal disease
Diabetes mellitus	Clinical measures
Obesity	Radiographic measures
Hypertension	Antibodies titers
Hyperlipidemia	Self-reported Questionnaires
Advanced age	Diversity of the studied population (age, ethnicity, diet, geographic area, socio-economic status)
Male gender	
Genetic predisposition	
Lack of physical activity	
Depression	

Table 3. Positive epidemiological evidence for the association between periodontitis and CAD

First Author (year) [REF]	Type of study (duration)	Sample size	Main Finding
Mattila (1989) [20]	Case-control	100 vs. 102	Association between recent myocardial infarction and total dental index
De Stefano (1993) [21]	Retrospective (14 years)	9,760	Severe vs. mild disease: 25% relative risk increase
Beck (1995) [22]	Prospective (4 years)	1,147	50% increase in the risk for CAD in severe periodontitis patients
Mattila (1995) [23]	Prospective (7 years)	214	In CAD patients dental health predicted incident fatal and nonfatal coronary events
Morrison (1999) [24]	Retrospective (20 years)	21,500	Severe gingivitis predicted for fatal CAD with adjusted OR of 2.15, whereas edentulous status with adjusted OR of 1.90
Jansson (2001) [25]	Prospective (27 years)	1,393	In patients aged <45 years the RR for CVD was 2.70 in those with marginal bone loss of >10% compared to subjects with mean marginal bone loss ≤10 %.

CAD, coronary artery disease; OR, odds ratio; RR, relative risk; CVD, cardiovascular disease

excluded definitively. A final concern raised by the pioneer Scandinavian study might be that it was limited in a very small geographical area, included only men and thus generalization in other populations with different demographic characteristics could not be easily projected.

Many other studies both positive (**Table 3**) [20-15] and negative (**Table 4**) [26-30] have been conducted after controlling for different overlapping risk factors and recruiting populations free of CAD. Although in these associations the outcome was well-defined, the determinant variable (i.e. periodontal measures) varied significantly among the studies. Indeed, teeth loss, radiographic assessed bone loss, and self-reported questionnaires constituted different expressions of periodontitis convicting the validity of the investigated association.

Association of periodontitis with surrogates of atherosclerosis

Another line of evidence highlighted significant

Table 4. Negative epidemiological evidence for the association between periodontitis and CAD

First Author (year) [REF]	Type of study (duration)	Sample size	Main Finding
Joshipura (1996) [26]	Prospective (6 years)	44,119	No relationship with CAD after adjustment for dietary risk factors
Howell (2001) [27]	Prospective (12 years)	22,037	Reported PD vs. no PD: no difference in CAD
Mattila (2000) [28]	Case – control	85 vs. 53	CAD patients vs. controls demonstrated the same magnitude of PD measures after careful adjustment for confounders
Hujoel (2001) [29]	Prospective NHANES I	4,027	Risk of CAD for those with PD: no difference with edentulous
Hujoel (2001) [30]	Prospective NHANES I	8,032	PD: no association with coronary events

CAD, coronary artery disease; PD, peridontal disease

correlations between periodontitis and intermediate end-points of vascular disease such as intima-media thickness [31], arterial stiffness [32], endothelial dysfunction [33-35] and albuminuria [36]. The emerging finding of a positive association between periodontal disease measures and blood pressure levels [37, 38] need to be further analyzed in future studies.

In the study by *Tonetti et al* [33] almost 100 patients with severe periodontitis were randomized in intensive and standard treatment for periodontal disease. Before any treatment, measures of endothelial function, systemic inflammation and molecular mediators mainly derived by endothelial cells were assessed. The two arms of the treatment were followed for 6 months and at the end of the study those underwent intensive treatment demonstrated ameliorated endothelial mediated dilation and decreased e-selectin levels in the context of lower count of neutrophils as compared with the standard periodontal therapy group. Interestingly, the two groups resulted with similar levels of high sensitivity C reactive protein at the end of the follow-up period. Just after the completion of the periodontal treatment it was noticed an acute deterioration of flow-mediated dilation and inflammation markers suggesting an acute systemic reaction to bacteremia. Taken together the above, periodontal treatment is accompanied by ameliorated endothelial function, and ephemeral bacteremia induced-inflammation is accompanied by acute deterioration of endothelial function.

Impaired endothelial function by the means of endothelial-dependent forearm blood flow was also detected in healthy and hypertensive patients with periodontitis as compared to their control counterparts, respectively. In that latter study, *Higashi et al* [34] demonstrated that their findings are probably due to the reduced bioavailability of nitric oxide in both groups (i.e. normotensive and hypertensive) affected by periodontitis. Non-endothelial mediated vasodilation was not affected by the presence of periodontitis, a finding in line with that of *Tonetti et al* [33]. Over a six-month follow-up period, treatment of periodontis resulted in amelioration of endothelial function, whereas non-treatment was accompanied by the same extent of endothelial dysfunction.

By using a cross-sectional design in never-treated newly diagnosed hypertensive patients without co-morbidities including diabetes mellitus and impaired glucose tolerance, we demonstrated that periodontal disease indexes (i.e. mean clinical loss of attachment, maximum probe depth, and gingival bleeding index) were associated with the levels of high sensitivity C reactive protein, asymmetric dimethyl-arginine and urinary albumin excretion [35, 36]. The pattern of higher levels of asymmetric dimethyl-arginine and C reactive protein was associated with more impaired periodontal disease indexes as compared with the lower levels' pattern of the same molecular surrogates. Additionally, periodontal disease indexes and C reactive protein levels synergistically determined urinary

albumin excretion in that cohort of hypertensive patients. These findings suggested a direct cross-talk between teeth and kidneys beyond the levels of systemic inflammation and hemodynamic load.

The cross-sectional arm of the INVEST (Infections and Vascular Disease Epidemiology Study) suggested that patients aged less than 65 years demonstrate an association between number of missing teeth and prevalence of carotid plaques, a finding not observed in those edentulous and aged over 65 years [39]. Additionally, radiographically assessed bone loss was associated with the same atherosclerosis-oriented outcome with the exception of the edentulous status [40]. Intima-media thickness was associated with the higher tertile of etiologic periodontal pathogens, over and above the levels of systemic inflammation in another cohort of the INVEST [41]. Finally, the level of office systolic and diastolic BP was higher in those at the higher tertile of etiologic periodontal pathogens as compared with the lower tertile. Putative pathogens of periodontal disease did not demonstrate correlation with the office hemodynamic load, whereas the tertiles of ecologic periodontal bacteria had an inverse correlation with office BP [37].

Facts and expectations

Up to date the etiological association between periodontitis and CAD remains by far unfulfilled. Statistical association between these phenomena probably exists, but even among these lines the majority of the studies so far did not implement clear measurements of the exposure variable (i.e. focal periodontitis measures), did not account appropriately for effect modifiers, whereas the outcome was addressed vaguely or simply by means of surrogate endpoints of atherosclerosis. Pathophysiological evidence suggests that ephemeral bacteremia accompanied by reactive periodical systemic inflammation and immunopathological reactions could conjointly interfere with vascular properties rendering cardiovascular system vulnerable to clinical events. However, many pathophysiological steps of the potential association between periodontits and CAD should be further clarified. Finally, from the clinical point of view there is not enough evidence to support prevention of CAD via periodontal disease prevention or treatment. As suggested in a recent consensus paper [16] in periodontal health and cardiovascular disease, the former should be promoted as part of a healthy lifestyle and hence as an important component in the prevention of cardiovascular disease. Contributors of the consensus paper clearly declare that there is not compelling evidence that preventive periodontal care or therapeutic intervention would influence cardiac health and accordingly it is not advisable to promote the message of oral health with the specific goal of preventing cardiovascular events.

Randomized controlled trials, using populations at higher risk for future cardiovascular events, with more severe periodontal disease might enlighten us as regards several unresolved issues on the association between periodontitis and CAD. To implement such a project, close collaboration of cardiologists and periodontologists is imperative and the design of future studies should appropriately assess the extent of the exposure variable [16, 42].

Conclusions

Periodontitis constitutes an active lever for systemic subclinical inflammation enhancement and eventually contributes to endothelial and vascular dysfunction. There is some evidence suggesting that periodontal pathogens could modulate the initiation and perpetuation of atherosclerosis. Up to date there is no compelling evidence that preventive periodontal care or even therapeutic intervention would influence cardiovascular health. Although etiological association between periodontitis and CAD is not supported by the present evidence, future investigation should not be discouraged given that these two entities are highly prevalent in both developed and developing countries and adversely contribute to the overall public health.

Conflict of interest: none for all authors.

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