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Review Article

Periodontitis and risk for atherosclerosis: an update on intervention trials

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Abstract

Aims: Periodontitis has been associated with an increased risk of cardiovascular events. The nature of the association is unclear because both periodontitis and cardiovascular disease (CVD) share a host of risk factors. Intervention trials are critical to explore the relationship. If the association were causal, successful periodontal therapy will lead to an attenuation of the effect – CVD.

Material and Methods: The paper reviewed the design and the results of intervention trials aimed at improving systemic inflammation, endothelial dysfunction, carotid atherosclerosis and cardiovascular events.

Results: Early systematic reviews and a definitive controlled clinical trial indicate that intensive periodontal therapy results in a decrease in systemic inflammation and an improvement of endothelial dysfunction in systemically healthy subjects. A pilot trial has indicated the feasibility to assess the impact of periodontal therapy on carotid atherosclerosis in a primary cardiac prevention design.

Conclusions: Efforts to test causality in the relationship between periodontitis and CVD are ongoing. Evidence to date is consistent with the notion that severe generalized periodontitis causes systemic inflammation and endothelial dysfunction. Periodontitis has effects that go beyond the oral cavity and its treatment and prevention may contribute to the prevention of atherosclerosis.

Key words: atherosclerosis; causality; controlled clinical trials; periodontitis; review

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In the last 50 years, cardiology has witnessed tremendous progress in the understanding of the risk factors for atherosclerosis and cardiovascular diseases (CVD). In spite of such enormous progress, a decade ago, it was highlighted that almost one out of two heart attacks are occurring in subjects without the classic Framingham study cardiovascular risk factors: high lipids, hypertension, diabetes and smoking (Braunwald 1997). The recognition that much is still to be learnt about the pathogenesis of atherosclerosis has provided strength to research approaches into alternative causes of atherosclerosis.

As it is understood today, atherosclerosis occurs in response to injury of the vascular endothelium (Ross 1999). Furthermore, the nature of the process is inflammatory (Libby 2002).

An important hypothesis in cardiology has been that chronic infections may contribute to atherogenesis. The validity of this hypothesis has been confirmed by studies indicating that subjects exposed to chronic infections have two to three times higher odds of having carotid atherosclerosis (Kiechl et al. 2001). Chronic obstructive pulmonary diseases with infectious exacerbations, chronic bronchitis, chronic sinusitis, chronic/recurrent urinary tract infections – but also an amorphous group of ''other'' infections – were all associated with higher odds of carotid atherosclerosis. Pathogens sustaining these chronic infections were considered to either have a direct effect on the vasculature or to exert an effect acting as a source of systemic inflammation that in turn would trigger the atherosclerotic process. Indeed, epidemiological studies linking systemic inflammation and atherosclerosis and cardiovascular events have shown consistent associations between levels of systemic inflammatory markers and increases in carotid intima-

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media thickness (IMT), myocardial infarction and non-haemorrhagic stroke.

Interest in the infectious/inflammatory hypothesis of atherosclerosis led a group of cardiologists in Finland to look into the relationship between oral health and myocardial infarction (Mattila et al. 1989). Since those early reports, debate has been raging with regard to the existence and nature of an association between periodontal disease and atherosclerotic CVD.

Several well-designed pre-clinical studies have indicated possible mechanistic explanations for the association between periodontal infections and atherosclerotic CVD (Li et al. 2002, Lalla et al. 2003, Brodala et al. 2005). The association is therefore biologically plausible and thus emphasis has been generally given to the strength and the consistency of the findings.

The majority of epidemiological studies have shown the presence of a significant association between periodontitis and myocardial infarction and stroke. Such studies usually report a moderately increased risk of CVD in subjects with periodontitis (odds ratios (OR), relative risks or hazard ratios ranging between 1.2 and 3.9). A lower risk has in general been presented in models corrected for other known risk factors (Humphrey et al. 2008).

Since the epidemiologic data were reported, the debate has centred on whether or not the association is: (1) real or due to residual confounding (e.g. by cigarette smoking: a common risk factor for both CVD and periodontitis) and (2) causal in nature (i.e. periodontitis contributes to the causal path leading to atherosclerosis and/or cardiovascular events). Both issues can only be fully addressed by intervention trials: randomized-controlled clinical experiments that seek to achieve an attenuation of the effect (atherosclerosis, cardiovascular events) through the elimination of the ''cause'' or exposure (periodontitis).

The aim of this paper is to review recent intervention trials exploring the causal relationship between periodontitis and systemic inflammation as well as the early stages of atherosclerosis.

Periodontitis and Systemic Inflammation

The fact that local production and accumulation of inflammatory mediators is the major mechanism leading to periodontal attachment loss and bone loss has been well established in the late 1980s (Williams et al. 1989). A series of studies in experimental animals and humans have shown that the administration of Non-Steroidal Anti-Inflammatory Agents significantly blocks periodontal destruction in subjects with naturally occurring periodontitis. Local levels of inflammatory mediators have been used as markers for active periodontal breakdown.

The systemic effect(s) of this local inflammatory reaction, however, have been largely neglected in the periodontal literature until the mid 1990s.

More recently, it has been noted that periodontal pathogens are able to invade gingival tissues (Papapanou et al. 1994), and from there, are able to gain access to the systemic circulation. It is well established that periodontal pathogens can cause severe systemic infections such as brain abscesses (Marques da Silva et al. 2004, Ewald et al. 2006), pulmonary infections (Latronica & Shukes 1973, Suzuki & Delisle 1984, De Soyza et al. 2000), cardiac infections as well as endovascular or orthopaedic prosthetic infections. Such infections occur as a result of the diffusion (haematic or respiratory) and establishment of periodontal pathogens in locations remote from the oral cavity. There, the bacteria are able to cause disease in these distant locations. Highly relevant to CVD is ex vivo evidence that has established the presence of DNA from periodontal pathogens in atherosclerotic plaques retrieved following endoarterectomies at the time of interventional cardiology procedures in subjects with periodontitis and evidence of periodontal colonization with the same bacterial species.

Furthermore, subjects with periodontitis present changes in their systemic inflammatory parameters: not only do periodontitis patients have increased local periodontal inflammation but they also have higher inflammation in their bloodstream. When compared with periodontally healthy subjects, patients with periodontitis have higher circulating numbers of granulocytes or higher concentrations of acute-phase markers such as C-reactive protein (CRP) (but also fibrinogen, serum amyloid and a host of cytokines).

In a recent meta-analysis of case–control studies, Paraskevas et al. (2008) found that subjects with periodontitis have 1.7 [95% confidence interval (CI) 1.1–2.2] mg/l higher serum CRP concentrations as compared with subjects without periodontitis. The magnitude of the difference is clinically significant as it is large enough to shift subjects between the identified classes of CRP-associated cardiovascular risk. The magnitude of the periodontitis-associated systemic inflammatory response is at the basis of the hypothesis that sees periodontitis as a contributor to the systemic inflammatory burden of the subject (Beck et al. 1998).

In more recent years, a series of intervention trials have sought to assess the causality between periodontitis and the observed increase in systemic inflammation.

An initial cohort study showed that periodontal therapy consisting of oral hygiene instructions, scaling and root planing and extraction of hopeless teeth can result in a dose-dependent improvement in systemic interleukin (IL)-6 and CRP: the better the clinical outcome of periodontal therapy, the larger the magnitude of the decrease in systemic markers of inflammation (D'Aiuto et al. 2004a, b).

Such initial data led to the performance of two small pilot trials to optimize the treatment regimen for maximal improvement of systemic parameters. Intensive periodontal therapy – defined as the combined application of oral hygiene instructions, extraction of hopeless teeth, scaling and root planing under local anaesthesia performed over a 24-h period and local controlled delivery of minocycline at all pockets 4 mm or deeper – led to better and earlier improvements as compared with conventional mechanical debridement alone (D'Aiuto et al. 2005, 2006).

A recent meta-analysis of these pilot intervention trials has indicated that periodontal therapy resulted in a weighted mean reduction in serum CRP of 0.5 (95% CI 0.08–0.93) mg. These data are in agreement with the notion that periodontitis contributes to the systemic inflammatory burden and that periodontal treatment leads to clinically relevant improvements in systemic inflammation (Paraskevas et al. 2008). These findings are important because increased levels of serum CRP (but also of other inflammatory parameters) are excellent predictors of the development of atherosclerosis and myocardial infarction (Albert et al. 2002, Ridker et al. 2005, Sabatine et al. 2007).

On the other hand, these data must be interpreted with caution as they refer to systemically healthy subjects with

severe generalized periodontitis. It is unclear what the impact of less severe and widespread forms of periodontitis is or how clinically significant CVD interferes with these findings.

Periodontitis and Endothelial Dysfunction

Endothelial dysfunction is considered to be the first inflammatory change of the vascular endothelium leading to arteriosclerosis. An early case–control study indicated that subjects with periodontitis had higher levels of endothelial dysfunction measured as flow-mediated dilatation (FMD) of the brachial artery that matched controls (Amar et al. 2003). Two pilot studies reported that periodontal therapy seemed to lead to changes in endothelial dysfunction (Seinost et al. 2005, Elter et al. 2006).

A recent definitive trial sought to assess the effect of intensive periodontal therapy on FMD of the brachial artery (Tonetti et al. 2007). Systemically healthy subjects not taking medications with severe generalized periodontitis were randomized to a control treatment (oral hygiene instructions and supragingival ultrasonic debridement) or an intensive periodontal therapy (oral hygiene instruction, scaling and root planing and extraction of hopeless teeth). No changes in FMD were observed over a 6-month period in the controls; after intensive treatment, however, there was a biphasic change in FMD: in the first days following treatment, there was a worsening of the systemic outcome, followed by an improvement compared with baseline and the control group. At the end of the trial, FMD in the test group was significantly better than in he control but also significantly better than at baseline, indicating that periodontal therapy led to an improvement of endothelial dysfunction in these subjects. The effect of treatment was dose dependent: there was a significant correlation between the reductions in the number of periodontal pockets and bleeding on probing and the improvement in endothelial function. In parallel to the changes in endothelial function, periodontal therapy led to changes in inflammatory and cardiovascular biomarkers, further strengthening the results of the trial with the indication of plausible mechanisms. This trial was the first confirmation of a causal link between an early functional cardiovascular parameter and periodontitis. It is important to highlight that these results were obtained in a subject population that was systemically healthy and affected by severe generalized periodontitis: the effect of systemic conditions or the impact of less widespread and severe periodontitis is still to be determined.

Periodontitis and Carotid Atherosclerosis

Among parameters of atherosclerosis that can be measured easily, carotid atherosclerosis, early atherosclerosis of the carotid, is frequently measured as an increase in the thickness of the IMT of the arterial wall. Measurement of this parameter has received considerable attention as it is highly correlated with disease in the coronary arteries as well as the cerebral arteries and thus is a good predictor of both cardiovascular and cerebrovascular ischaemic events.

In the context of the Atherosclerosis Risk in Community Study, subjects with severe generalized periodontitis had higher odds (OR 1.3, 95% CI 1.03–1.66) of having carotid IMTof 1 mm or more after correcting for other known factors. Interestingly, the study reported that subjects with severe generalized periodontitis had a higher risk than those with less widespread disease, suggesting the possibility of a dose-dependent effect of the exposure (Beck et al. 2001). In a follow-up study of the same material with a better definition of bacterial exposure using serum immunoglobulin G (IgG) antibodies against oral microorganisms, higher chances of having carotid atherosclerosis were observed among subjects with elevated antibody titres to *Campylobacter rectus* and *Peptostreptococcus micros* (Beck et al. 2005). Interestingly, this association was present in both smokers and never smokers, suggesting that smoking did not act as a confounder or an effect modifier in this association.

A recent pilot study reported the effect of periodontal therapy on changes in carotid IMT (Piconi et al. 2009). A group of otherwise healthy individuals affected by mild to moderate periodontitis was treated with root debridement. Six and 12 months later, IMT was significantly decreased at different locations in the carotid artery. These pilot observations indicate that changes in IMT following periodontal therapy are possible in systemically healthy subjects and provide important information for the design of properly designed and sized intervention trials.

Periodontitis and Cardiovascular Events

Periodontitis is associated with cardiovascular events and non-haemorrhagic stroke. Intervention trials aimed at assessing whether or not periodontal therapy decreases the risk for cardiovascular pose formidable challenges in terms of size of the study, length of follow-up (with associated ethical issues), co-morbidity, concomitant medications, delivery of effective treatment and supportive periodontal care. To effectively address some of the issues, the Periodontitis and Vascular Events (PAVE) study was designed and executed in pilot form. PAVE was a secondary cardiac prevention trial: it enriched the probability of cardiovascular events by recruiting subjects who had suffered from a first myocardial infarction or who had symptoms of angina and in these subjects aimed at reducing the risk of a future event (Beck et al. 2008, Couper et al. 2008). The study was aimed at assessing the feasibility to perform a definitive study with such a design in a co-ordinated cardiac and dental centre setting. Subjects in the study received either community care or scaling and root planing according to protocol. The results of the study indicated that the intervention did not perform well in terms of periodontal outcomes: no significant differences could be demonstrated between the test and the control groups. Furthermore, the level of improvement fell short of established clinical standards, thus highlighting the challenges of secondary cardiac prevention trial designs (Offenbacher et al. 2009). Obviously, failure of the intervention requires careful interpretation of the negative results of intervention trials: lack of attenuation of the effect may not be an indication of a lack of a cause and effect relationship between periodontitis and atherosclerotic diseases (Armitage 2008).

Conclusions

Data from recent intervention trials indicate that periodontal treatment seems to attenuate systemic inflammation and endothelial dysfunction (the first step in the process leading to atherosclerosis).

Taken together, data show a dose-dependent effect: better periodontal treatment outcomes seem to be associated with more significant changes in the systemic parameters. Periodontitis may contribute to the systemic inflammatory burden and process leading to atherosclerosis in otherwise healthy individuals.

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Clinical Relevance

Scientific rationale for the study. To establish whether a causal link exists between periodontitis and atherosclerosis, intervention trials are essential: if periodontitis is treated – and it is causally linked to atherosclerosis – an attenuation of the effect (CVD) is expected.

Principal findings. Intervention trials and early meta-analysis have indicated that periodontitis is a cause of systemic inflammation and endothelial dysfunction – the first step in the atherosclerotic process.

Practical implications. Periodontal infections have effects that go beyond the oral cavity in subjects affected by severe forms. Periodontal prevention and treatment may contribute to general health.