



Is There A Link Between Periodontitis and Cardiovascular Disease?

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Is There A Link Between Periodontitis and Cardiovascular Disease?



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INTRODUCTION

Dentistry, the Media, Our *Hearts* and Minds

There has been a groundswell of information in the various media that have highlighted the possibility that there may be correlations between heart or cardiovascular disease and periodontitis. Indeed, the prevailing type of report from the media is one that is somewhat alarmist to say the least, and misleading at worst.

In this regard, we must recognize that there do appear to be statistical associations between periodontitis and cardiovascular disease as described in this article. But when these associations are looked at more closely, they do not appear to be as robust as we might have thought. Indeed, concepts have come to light suggesting that the apparent correlations between periodontitis and cardiovascular disease may be related to the possibility that patients who are at risk for one disease may be genetically at risk for the other. This may be particularly so if such patients are exposed to the same epigenetic risk factors known to play a role in both disorder groups, e.g. smoking.

In order to understand the putative relationships between periodontitis and cardiovascular disease, it is essential to understand some fundamental issues pertaining to their epidemiological, pathophysiological, and microbiological characteristics.

Epidemiology of Periodontitis and Cardiovascular Disease

According to the most recent National Health and Nutrition Examination Survey (NHANES III) carried out between 1988 and 1994, 34.5% of dentate U.S. citizens 30 years or older had periodontitis. The prevalence of periodontitis increased with increasing age (Albandar et al, 1999) and in developed countries, cardiovascular disease accounts for 50% of deaths (WHO report, 1995) and is considered the number one cause of death in the U.S. (Rosenberg et al, 1996).

These data are consistent with the notion that both diseases are relatively prevalent and, as such, these findings could confound studies that seek to demonstrate a true relationship between cardiovascular disease and periodontitis (statistical alone or actually causal). Nevertheless, there are now several studies that seem to indicate that there are associations between cardiovascular disease and periodontitis.

Epidemiological Studies: Link Between Periodontitis and Cardiovascular Disease

A number of studies have shown an association between oral conditions and atherosclerosis and coronary heart disease.

According to DeStefano et al., patients with periodontitis have a 25% increased risk of coronary heart disease relative to those without it (DeStefano et al, 1993). Periodontal disease was shown to be a stronger risk factor in men younger than 50 years at baseline, with a relative risk of 1.72. In this particular study, the periodontal index was used to assess exposure to periodontitis and the main outcome evaluated was hospital admissions and deaths related to coronary heart disease.

Beck et al. conducted a cohort study using combined data from the Normative Aging Study and the Dental Longitudinal Study sponsored by the United States Department of Veterans Affairs. The study found that the incidence odds ratios for bone loss and total cardiovascular disease, fatal cardiovascular disease and stroke were 1.5, 1.9, and 2.8 respectively, after adjustment for established cardiovascular risk factors. For every 20% increase in bone loss, the incidence of total cardiovascular disease increased by 40% (Beck et al, 1996).

After completing a case control study with 303 patients examined within seven days after acute ischemic stroke or transient ischemic attack (Grau et al, 2004), it was further concluded that periodontitis is an independent risk factor for stroke. Subjects with severe periodontitis had 4.3 times higher risk for cerebral ischaemia than subjects with mild or without periodontal disease (Rosenberger et al, 1996).

The weight of epidemiological evidence, then, seems to support the concept that periodontitis and cardiovascular disease co-present and may predict one another's presence. The studies still do not indicate, however, that there are causal associations between the two diseases; or even if there are causal associations, whether they are bi-directional as has been demonstrated with diabetes.

That said, the lack of bi-directional effects does not rule out the possibility that periodontitis might play a causal role in cardiovascular disease, or at least exacerbate cardiovascular disease processes such as inflammation. Indeed, there is good evidence to indicate that atherosclerosis, and in particular, atherosclerotic lesions were once considered as bland lesions. However, at this time there is good evidence to suggest that atherosclerosis is, in fact, an inflammatory disease with correlations to c-reactive protein levels as also shown in periodontitis. Hence, certain inflammatory mediators that are produced in periodontal lesions are found in the bloodstream, e.g. prostaglandins, and these could conceivably contribute to remote inflammatory lesions such as atherosclerotic plaques.

Thus, there is biological plausibility with regard to the notion that periodontal lesions

could lead to exacerbation of atherosclerosis and hence coronary artery disease for example. Biological plausibility notwithstanding, one must also consider that the risk factors for periodontitis are, in many cases, similar to those reported for cardiovascular disease. Could it be then that similar risk factors, when present, might, in a susceptible individual, trigger both cardiovascular disease and periodontitis?

Risk Factors: Periodontitis and Cardiovascular Disease

The difficulty in drawing a cause and effect relationship between periodontitis and cardiovascular disease stems from the fact that the two groups of diseases share many risk factors. Risk factors, such as smoking, genetics, stress and increasing age, could independently lead to periodontal disease and to cardiovascular disease in a group of patients, possibly leading to the incorrect assumption that the two diseases are linked (Hujoel et al, 2002).

It was also suggested that statistical adjustment for confounding risk factors, such as smoking, may not be adequate and a population of non-smokers who actually *never* smoked should be evaluated (Hujoel et al, 2002). In studies where adjustment for smoking dose (cigarettes per day) was included in the analysis, the relationship between periodontitis and cardiovascular disease was shown to be insignificant. None of the studies to-date demonstrated a link between periodontitis and cardiovascular disease in non-smokers (Hujoel et al, 2002).

Inflammatory Mediators: IL-1, TNF, MMP

Immune response and inflammatory cascade are characterized by the upregulation and release of inflammatory cytokines that exert their effect on the local tissues. Important mediators of inflammation include nuclear factor-kappa B (NF- κ B), interleukin-1 (IL-1), tumour necrosis factor alpha (TNF- α), matrix metalloproteinases (MMPs), c-reactive protein (CRP), interleukin-6 (IL-6) and interferon gamma (IFN- γ).

In periodontal disease and cardiovascular disease, the cellular sources of these inflammatory mediators are very similar. The monocytes/macrophages, lymphocytes, polymorphonuclear leukocytes, mast cells, fibroblasts, and endothelial cells in both diseases release these inflammatory mediators. Some differences are that the epithelial cells and osteoblasts produce inflammatory mediators in periodontal disease, while smooth muscle cells also produce these mediators in cardiovascular disease.

Three notable mediators that lead to tissue destruction and disease are IL-1, TNF- α and MMPs. Both IL-1 and TNF- α are pro-inflammatory cytokines and are produced by several cells types with a diverse array of activities. Studies have demonstrated that they are involved with inflammation and connective tissue breakdown and can limit

repair of periodontium and myocardium. Specifically, their role in inflammation includes the stimulation of adhesion molecule and chemokine expression, and production of other inflammatory mediators such as prostaglandin E2. They also limit repair of the periodontium and myocardium by stimulating apoptosis matrix producing cells and increase connective tissue breakdown through induction of matrix metalloproteinases expression (Graves and Cochran 2003).

The hallmark of periodontal and cardiovascular diseases is connective tissue degradation, specially, collagen breakdown. The matrix metalloproteinases are the primary enzyme that leads to collagen breakdown. In periodontitis, these enzymes degrade the periodontal connective tissue, which ultimately leads to tooth loss. Similarly, in atherosclerosis, these enzymes degrade the fibrous cap, which may lead to a myocardial infarction.

Infection and Atherosclerosis

It has been established that the development of atherosclerotic plaques throughout the body, and in particular the cardiac vessels, is associated with a number of potential risk factors. Generally, it has been assumed that atherosclerotic plaques form as a result of the accumulation of low-density lipoprotein (LDL) cholesterol in the arterial wall. However, it has been noted that the formation of the lesion is due to a complex series of events, reminiscent of an inflammatory reaction (Ross, 1999). The origin of this inflammatory reaction has led to the consideration that infection may be a component of the mechanism that results in the development of this lesion.

An elevated level of c-reactive protein, a non-specific marker of inflammation, has been associated with an increased risk of cardiovascular disease. Elevated levels of pathogens, either individually or as a cumulative “pathogen burden” have correlated with elevated c-reactive protein levels (Zhu et al, 2000b). Pathogens that have been investigated include *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex virus (HSV), hepatitis A virus (HAV), cytomegalovirus (CMV), as well as more recent investigation into the effects of putative periodontal pathogens on the development of cardiovascular disease.

A number of studies have looked at the effect of *Chlamydia pneumoniae* and the incidence of cardiovascular disease. Since the late 1980s, it has been suggested that elevated antibody levels and immune complexes containing *C. pneumoniae* were detected in acute MI patients (Saikku et al, 1988). More recent studies have suggested a 2 to 4-fold increased prevalence of cardiovascular disease when anti- *C. pneumoniae* antibodies were detected (Danesh et al, 1997). Other lines of evidence implicating *C. pneumoniae* include the identification and culture of viable *C. pneumoniae* organisms from atheroma, animal models with *C. pneumoniae* –induced atherogenesis as well as

the growth of *C. pneumoniae* in vascular cells *in vitro* (Gupta, S, 1999).

However, not all investigations point to this conclusion. Nieto suggested that data from the Atherosclerosis Risk in Communities Study indicated that IgG antibody titers to *C. pneumoniae* were elevated in both cardiovascular disease and non-cardiovascular disease participants (Nieto et al, 1999). Based on samples following carotid endarterectomy, it was demonstrated that *C. pneumoniae* did not play a causal role in the progression of disease in an advanced carotid atherosclerosis population (Jahromi et al, 2003).

Finally, one of the most anticipated intervention trials, the WIZARD study (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders), a randomized placebo-controlled trial, assessed the effects of antibiotic therapy on coronary heart disease events in patients with stable coronary artery disease and known *C. pneumoniae*- exposure. Subjects were placed on a 12-week course of azithromycin to assess whether or not a reduction in cardiovascular-related events occurred. The study did not demonstrate any significant differences between the drug and placebo group with respect to the incidence of future cardiac-related events, thereby further questioning the role of *C. pneumoniae* (and perhaps other infection) in cardiovascular disease (O'Connor et al, 2003).

As previously noted, many other pathogens have been investigated as to their potential contribution to cardiovascular disease. It has been shown that there was an increase in the association between the presence of serum IgG antibodies to Hepatitis A virus (HAV) and coronary artery disease (Zhu et al, 2000b). The same investigators also noted that the level of c-reactive protein was elevated in patients with coronary artery disease (one of the presentations of cardiovascular disease) (Zhu et al, 2000a). Apparently, while IgG antibodies to *C. pneumoniae* and Herpes Simplex-1 (HSV-1) have been associated with a 2-fold increase in the risk of myocardial infarction and coronary heart disease, the presence of IgG antibodies to CMV was not associated with that increase (Siscovick et al, 2000).

However, through all of this, it appears that rather than looking for a single pathogen, researchers are focusing efforts on assessing the total pathogen burden and its effects on cardiovascular disease, myocardial infarction and death. The pathogens selected for study were chosen due to the fact that they shared common characteristics: all were obligate intracellular pathogens; all established persistent antibodies targeted to the pathogens; many establish a life-long persistence or latency period or at least demonstrate life-long presence of antibodies, as is the case of HAV.

However, what does appear to be consistent throughout the studies is the elevated level of c-reactive protein and its association with cardiovascular disease. This

elevated level of c-reactive protein appears to be brought on by an increased overall pathogen burden rather than any one individual pathogen (Zhu et al, 2001).

As already discussed, epidemiological studies since the 1980s have implicated periodontitis as a risk factor for cardiovascular disease (Matilla KJ et al, 1989). Yet, the direct role of periodontal pathogens as mediators of cardiovascular disease still needed to be established.

Biologically plausible mechanisms that could link periodontal and cardiovascular diseases (Herzberg and Meyer, 1996) suggested that *S. sanguis* might directly contribute to platelet aggregation and the development of thrombi, which could conceivably contribute to an acute myocardial infarct. This was also suggested by others who showed that multiple infectious agents, including *P. gingivalis* and *S. sanguis*, may be isolated from atherosclerotic plaques taken from human carotid endarterectomy specimen (Chiu B, 1999, Haraszthy et al, 2000). Along similar lines, recent data suggested the presence of a combined antibody response to *P. gingivalis* and *A. actinomycetemcomitans* were associated with an odds ratio of 1.5 for coronary heart disease. Interestingly, the robustness of the antibody response also appeared to correlate with an increase in the odds ratio for cardiovascular disease (Pussinen et al, 2003).

The question remains as to whether or not the presence of the bacteria indicates they play an active role in the development of atherosclerotic plaques, or are they merely the by-products of DNA travelling through the system. It has been suggested that components of bacteria, i.e. outer membrane vesicles, contain virulence factors (toxins, lipopolysaccharides) that may contribute to the development of atherosclerotic plaques.

However, more recent studies suggest that, although bacterial DNA may be present in atherosclerotic plaques, viable oral bacteria taken from carotid and femoral atherosclerotic plaque could not be identified (Fiehn et al, 2005).

At this point in time, the data accumulated indicating a direct linkage between periodontal pathogens and coronary heart disease seems equivocal at best. A systemic review of the literature published between 1966 and 2002, focusing on the influence that periodontal disease may have on the initiation/progression of cardiovascular disease, was reported relatively recently (Scannapieco et al, 2003). It was concluded that the literature supported only a modest association between atherosclerosis and periodontal disease. It was also suggested that further large-scale longitudinal studies are required to further investigate the association and determine if causality can be shown (Scannapieco et al, 2003).

In this regard, it must be recognized that there are multiple risk factors for

cardiovascular disease that are difficult to control for in clinical studies. Consider the case of cardiovascular disease in Third World countries where the presence of multiple species and more virulent types of bacteria thrive. Yet the incidence of cardiovascular disease is dramatically less than is seen in industrialized countries, where socio-economic factors have a larger influence. At this time, research continues to be “hypothesis-generating” rather than “hypothesis-proving.” More work is required in this field before treatment standards and protocols can be altered.

Other Common Aspects of Periodontitis and Cardiovascular Disease

One of the most intriguing notions with respect to the putative relationships between periodontitis and cardiovascular disease may be related to some of the similarities in their underlying pathophysiological and physiological regulatory systems. For instance, as has already been discussed, smoking is a significant risk factor for both diseases. Current data in our laboratories suggest that an important component of cigarette smoke, aryl hydrocarbons (Singh et al, 2000), have the ability to inhibit bone formation, particularly in the presence of periodontal disease causing bacterial co-factors (Andreou et al, 2004). As such, these data could help to explain, in part, how cigarette smoking might lead to periodontal bone loss.

Interestingly, we now also have data to suggest that these same aryl hydrocarbons may promote vascular disease, as measured by vascular calcification (Usman, O., MSc Thesis, University of Toronto, 2004). Thus, a common risk factor, smoking/aryl hydrocarbons, mitigates negative effects in two disparate systems: the periodontium and vascular tissues.

Along similar lines, it is also well-known that matrix metalloproteases (MMPs), including the collagenases, likely play an important role in periodontal tissue breakdown (Lee et al, 2004). Similarly, it is known that matrix metalloproteases also play a role in cardiovascular disease ranging from destabilization of atheromas to regulation of the development of heart failure and the deleterious changes in extracellular matrix in the myocardium (Francis et al, 2002). Again, one sees parallelisms between periodontal tissue destruction and cardiovascular disease, both mediated and/or regulated by a similar pathway, in this case one associated with MMPs. In fact, there is increasing evidence that inhibition of MMPs, already shown to be effective for inhibition of periodontal attachment loss, can also inhibit the development of cardiac failure (Matsumura S, et al, 2005).

In light of these common aspects, it is also conceivable that any relationships observed between cardiovascular disease and periodontitis could be related to the possibility that pathological or biological factors that adversely affect one system also adversely affect the other.

Conclusions

In light of the foregoing, it is essential that we recognize the possible links between periodontitis and cardiovascular disease. This link may, however, be related to several factors that transcend interdependency and a putative causal relationship between both diseases. Certainly, biologically plausible arguments and data have been presented that could explain this putative relationship, and even elucidate a possible causal association between both diseases. If a causal association exists though, it is probable one way unlike that seen in diabetes, i.e. periodontal diseases or at least associated pathogens might increase the risk of cardiovascular disease.

However, it is also possible that the apparent association between these two disease groups is related more to the existence of common risk factors and common underlying physiologies and pathophysiologies.

Unless and until definitive clinical studies can demonstrate or further explain the associations between periodontitis and cardiovascular disease, it is premature to counsel our patients to ‘floss or die.’

Periodontitis needs to be prevented and treated in its own right. Yet, by studying the apparent relationships between these two diseases, it is likely that we will learn even more about both!

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