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COMMENTARY

Chronic inflammation, periodontitis and cardiovascular diseases

AD Hingorani[1], F D'Aiuto[2]

[1]*Center for Clinical Pharmacology, University College London, London, UK;* [2]*UCL Eastman Dental Institute, Periodontology Unit, London, UK*

Chronic inflammation is seen in atheromatous plaques, the pathological substrate for coronary artery disease (Tracy, 1998; Libby *et al*, 2002). Extra-vascular inflammation because of chronic infection or autoimmune disorders, such as rheumatoid arthritis and systemic lupus erythematosus is associated with premature atherosclerosis (Bacon *et al*, 2002; Haque and Bruce, 2005; Sattar and McInnes, 2005). Acute inflammatory episodes, from intercurrent infection in the respiratory or urinary tract, or from surgical procedures, are associated with a transiently increased risk of acute atherothrombotic coronary events (Smeeth *et al*, 2004). Local inflammation in the damaged myocardium involving complement, neutrophils and monocytes may also contribute to the severity and consequence of ischaemic tissue damage following acute myocardial infarction or acute coronary syndrome (Pepys and Hirschfield, 2003). Thus, inflammation has been implicated at all stages in the natural history of coronary disease from the long slow process of atherogenesis, to acute atheromthrombosis as well as ischaemic myocardial damage.

In this issue of *Oral Diseases*, Sheilesh *et al* review the evidence linking periodontal and cardiovascular diseases. Their meritorious efforts in scoring the level of evidence supporting a causal association between periodontitis and cardiovascular disease support the notion that more research in this area is needed. After reviewing in detail most of the experimental pre-clinical studies on this topic, they suggest that it may be the host inflammatory response to periodontal pathogens, rather than the pathogens themselves causally linked to the development of atheroma.

Periodontitis is a chronic infectious disease affecting gingival tissues, periodontal ligament and alveolar bone and may be a potential source of systemic inflammation promoting atherogenesis. Its treatment relies upon the mechanical cleaning of the diseased dentition, which reduces local bacterial load and clinical signs of gingival inflammation (Pihlstrom *et al*, 2005). Cross-sectional and prospective epidemiological studies in humans have shown associations between the presence and severity of periodontal disease and circulating inflammatory biomarkers (Slade *et al*, 2000, 2003; Noack *et al*, 2001), endothelial dysfunction (Amar *et al*, 2003), subclinical atherosclerosis (Beck *et al*, 2001; Desvarieux *et al*, 2005) and cardiovascular outcomes (Bahekar *et al*, 2007). In animal models of atherosclerosis, inoculation with bacterial pathogens responsible for periodontal disease in humans, but not non-pathogenic mutant strains, leads to acceleration of atherosclerosis, providing biological plausibility to the hypothesis that periodontal infection might be a contributing factor in the development of coronary disease or stroke in man (Li *et al*, 2002).

However, it is still not known to what extent the bulk of information obtained from animal models can be directly referred to an *in vivo* situation in humans where a more complex web of signalling takes place. A number of mechanisms may be responsible for the relationship between periodontal and vascular diseases. Endothelium is a key signal transducer of processes that are involved in atherogenesis during the preclinical phase and also affecting plaque instability and clinical events. Evidence from a prospective survey on the pathogenesis of atherosclerosis suggests that endotoxin levels correlate well with carotid atherosclerosis and incident atherosclerosis (Wiedermann *et al*, 1999). The degree and severity of periodontitis also correlate with components of the metabolic syndrome (Shimazaki *et al*, 2007) that is itself a risk factor for atheroma (Grundy, 2007). As there is evidence that periodontal pathogens and their end-products may invade periodontal tissues and reach the bloodstream (Forner *et al*, 2006), it is plausible that they might cause direct damage to the endothelium (Libby *et al*, 1997), induce a host inflammatory response (Slade *et al*, 2003), increase lipoprotein oxidation (Mayr *et al*, 2006), induce alterations in systemic metabolism, or activate autoimmune processes relevant to atheroma

Correspondence: Dr Aroon D Hingorani, Centre for Clinical Pharmacology, Ground Floor, Rayne Institute, 5 University Street, London, WC1E 6JF, UK. Tel: +44 (0)20 7679 6612, Fax: +44 (0)20 7691 2838, E-mail: a.hingorani@ucl.ac.uk
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formation (Kol *et al*, 2000). Ultimately, the link between periodontal disease and atherosclerosis reported in observational studies in humans might not be causal, but might be explained by residual confounding (where the link occurs from a common association of periodontitis and heart disease with another causative factor such as cigarette smoking). Nevertheless, more recently, information is emerging from randomised trials in humans that the treatment of periodontal disease may have salutary effects. Such trials give important information on causal pathways as the randomised design results in a balancing of potential confounding factors such as cigarette smoking. In recent studies, treatment of periodontal disease has led to improvements in indices of the severity of periodontal disease, long-term improvements in endothelial function (after a short-term decline that corresponds to the acute inflammatory response to the treatment itself) and in some studies (but not all) beneficial alterations in circulating markers of inflammation and endothelial activation (Brunner *et al*, 2005; Seinost *et al*, 2005; Elter *et al*, 2006; Blum *et al*, 2007; Higashi *et al*, 2007; Tonetti *et al*, 2007). In non-randomised trials of periodontal therapy as well as in studies of patients with autoimmune disorders receiving immunosuppressant or biological therapies (e.g. anti-TNF alpha antibodies), similar improvements in endothelial function have been noted (Hurlimann *et al*, 2002; Gonzalez-Gay *et al*, 2006; Komai *et al*, 2007).

If the link between periodontal and coronary artery disease and stroke were causal, then treatment of periodontal disease would offer a new approach to the cardiovascular disease prevention. However, a number of issues need to be addressed before such an approach can be recommended. First, interventional studies have not delivered the same type of periodontal therapy, some including also the use of local or systemic antibiotics. The most effective form of periodontal treatment needs to be identified that balances the requirements of adequate treatment of the dental disease with widespread applicability in general dental practice. This treatment approach should be consistently used and included in the study design of future trials reports. Second, most studies have been of short duration (6 months) so it is uncertain if the reported vascular benefits that arise are sustained for the longer term. Third, a better understanding of the mechanisms involved in the improvement in vascular function following periodontal therapy should be pursued. Cross-sectional associations of periodontitis with blood pressure, lipids and the metabolic syndrome may mean that the benefit in vascular health observed in interventional trials (Tonetti *et al*, 2007) might be accounted for, in part, as a result of improvements in traditional cardiovascular risk factors (such as dyslipidemia, blood pressure and cigarette smoking), for which limited measures have been made. Alternatively, the improvements in vessel function might relate to reductions in the direct effect of circulating bacterial products on the vascular wall, and/or a reduction in the systemic inflammatory response to periodontitis. More detailed assessment of these and other potential pathways, e.g. oxidant stress, is now required. Such mechanistic studies may also uncover new, important disease mechanisms not relevant to oral diseases alone. Fourth, although endothelial function is regarded as being an early component of atherosclerosis that is strongly linked to clinical events (Deanfield *et al*, 2007), trials assessing other subclinical markers of atherosclerosis such as carotid intima media thickness are required. Finally, the final arbiter of the efficacy of periodontal therapy in the prevention cardiovascular events will be large-scale randomised trials in which major clinical disease events (heart attacks and stroke) are the outcome assessed.

The link between periodontitis and cardiovascular disease is an exciting example of the expanding link between oral disease and common systemic disorders of later life. Research in this area will require closer links between the medical and dental professions to help provide answers to the important unanswered questions that might offer new opportunities to improve public health.

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