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Understanding residual inflammatory risk sheds new light on the clinical importance of periodontitis in cardiovascular disease

The role of inflammation in mediating risk in atherosclerotic cardiovascular disease (CVD) has been highlighted by the CANTOS trial.[1] This showed for the first time, that in patients with established CVD, targeting chronic residual systemic inflammation after myocardial infarction, with Canakinumab, a monoclonal antibody against the interleukin (IL)-1 beta innate immunity pathway, reduced cardiovascular (CV) events in patients with high residual inflammatory risk identified by elevated high-sensitivity C-reactive protein (CRP) and IL-6 levels. Whilst the study established a causal role for inflammation in the pathophysiology of complications of atherosclerosis, discussion continues on the best approaches to target inflammation in a safe and sustainable way.[2]

Identifying and treating previously unrecognized but common sources of systemic inflammation causally associated with CVD could create a unique, safe, and cheap opportunity to reduce cardiovascular risk. Periodontitis (PD) represents one the most prevalent forms of chronic inflammatory diseases (both local and systemic) worldwide.[3] Recent surveillance surveys estimate that at least 40% of dentate adults, aged $\geq$30 years, have some form of PD and this rises to >60% in people >65 years.[4]

The majority of evidence linking PD to CVD has been derived from observational studies or small, underpowered, interventions.[3] In some of these studies, direct PD measurements were absent and surrogates were used to assess periodontal status, such as the presence of loose teeth or poor oral hygiene. In 2012, the American Academy of Periodontology issued a joint statement with the American Heart Association about the link between CVDs and PD: 'Observational studies to date support an association between periodontal pocket depth and atherosclerotic vascular disease, independent of known confounders. They do not, however, support a causative relationship' (*Figure 1*) .[5]

However, during the last 10 years, evidence from randomized clinical trials has demonstrated that intensive treatment of PD can reduce CV risk. We showed that a single session of intensive dental treatment to manage periodontal inflammation caused an initial systemic inflammation spike which was accompanied by deterioration in vascular endothelial function in the brachial artery. This was followed by a steady improvement in flow-mediated dilatation (FMD) over the next 6 months, as periodontal health improved.[6] Systematic appraisal of the evidence from the small intervention studies which followed, confirmed that successful treatment of PD produced a reduction of systemic inflammation especially in patients with other comorbidities such as Type 2 diabetes[7] and that both endothelial function and other phenotypes of atheroma (carotid Intima-Media Thickness (cIMT)) were improved.[8]

Our group has recently assessed the impact of improved periodontal health in a randomized clinical trial of patients with Type 2 diabetes and showed that PD treatment was associated not only with improved vascular endothelial function, as we had shown previously in patients without diabetes, but also in improved glycaemic control and renal function at 12 months. The benefits were linked to a progressive reduction of systemic inflammation assessed by C-reactive protein and tumour necrosis factor-α. These changes were independent of common CV risk factors and even of standard pharmacological regimens.[9] The mechanisms by which PD may result in adverse systemic effects are now of great interest.

In our studies, the degree of improvement in metabolic and vascular parameters was associated, in a linear fashion, with the magnitude of reduction of gingival inflammation and improved oral health (reflecting bacterial and inflammatory burden at the dento-gingival interface).[9,10] Previously, direct microbial effects on the vascular system had been postulated from interactions of circulating bacteria with the endothelium.[11] An alternative mechanism may be via systemic activation of the immune system, as a result of increased production of pro-inflammatory markers and cytokines.[12–17] There is also evidence of a significant decrease of pro-inflammatory cytokines and improvement of endothelial function after intensive periodontal treatment.[6]

Following this study, other groups have confirmed the beneficial influence of periodontal treatment on inflammatory markers as cytokines, CRP, as well as endothelial function.[7,10,18–20] Furthermore, rather than just a mere reduction of biomarkers of inflammation, recent evidence points to cellular pathways which are linked to vascular reactivity as exciting new mechanisms through which common sources of extravascular inflammation could influence the onset and progression of vascular disease.[10,21]

We have recently evaluated how the systemic effects of PD might affect blood pressure control. Previously, the evidence linking PD and hypertension was based on observational studies.[22–24] In a systematic review, we have shown that diagnosis of PD is associated with an average 20% increase in odds of having hypertension and an increase in mean systolic blood pressure (SBP) [weighted mean difference of 4.49 mmHg; 95% confidence interval (CI) 2.88–6.11] and diastolic blood pressure (2.03 mmHg; 95% CI 1.25–2.81) when compared to controls.[25] This has been followed by a Mendelian Randomization study in the UK-Biobank and International Consortium for Blood Pressure (ICBP)-Genome Wide Association Study (GWAS) datasets (including ~750 000 participants) to determine a possible causal relationship of PD with increased blood pressure, using previously GWAS-linked genetic variants as surrogates of lifetime risk of PD. Our group has performed the first randomized trial using ambulatory blood pressure as a primary endpoint in patients with inadequately controlled hypertension. One hundred and one patients with office blood pressure >140/90 mmHg despite stable antihypertensive regimen (using $\geq$1 medication for over 6 months) and concomitant moderate to severe PD were randomized 1:1 to receive intensive or control periodontal treatment. In the intensive therapy group, 2 months after treatment, we observed a reduction in blood pressure of 7.5 $\pm$ 10.5 mmHg. This was accompanied by improved endothelial function as assessed by FMD. It is interesting that the degree of SBP reduction

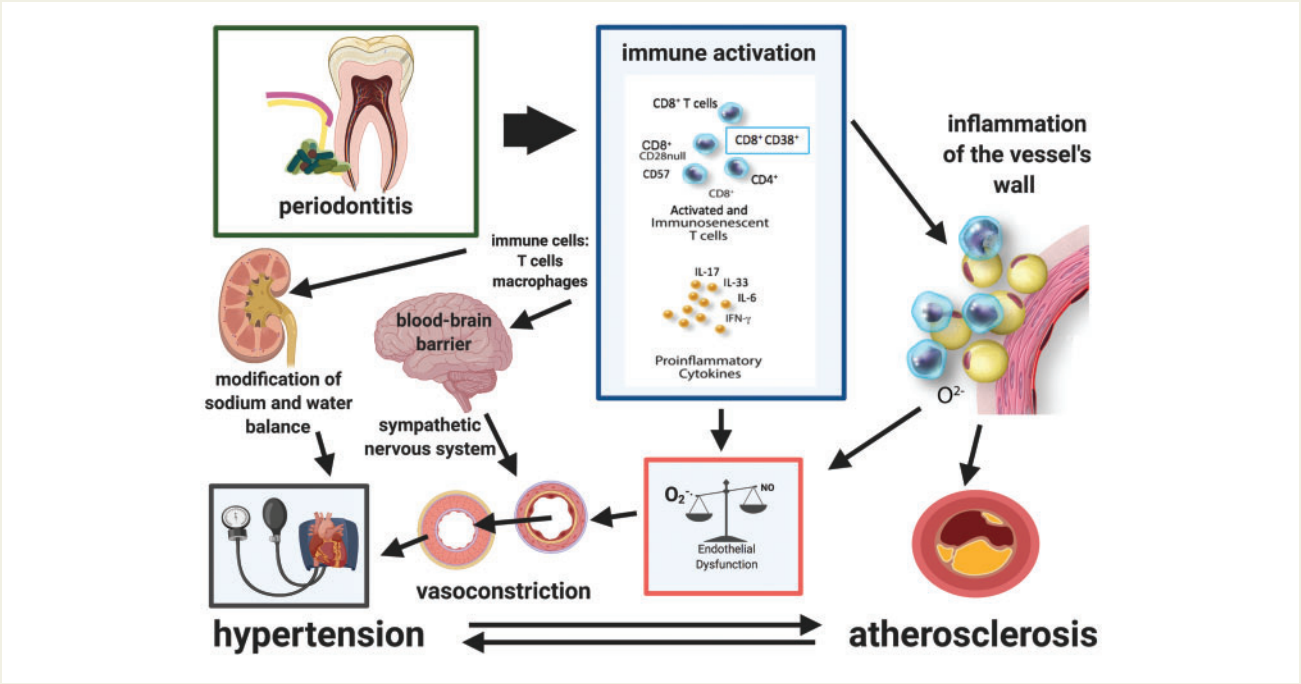

Figure 1 Multiple pathways underlying the potential mechanistic links between periodontitis and cardiovascular diseases. Created with BioRender as part of Academic License.

was most strongly correlated with the improvement in periodontal inflammation.[10] These findings raise the question of whether improving periodontal health could result in substantial blood pressure reductions in larger populations and importantly without changes in pharmacotherapy. In our randomized clinical trial, the blood pressure reduction was large, and this is consistent with the small number of intervention trials which measured office blood pressure (BP) after PD treatment.[16,26,27] In the most recent of these, the difference in BP between intensive and control periodontal therapy reached 12.5 ± 10.4 mmHg 6 months after successful periodontal treatment in patients with prehypertension.[28]

The pathophysiological mechanisms of the effects of PD on blood pressure regulation are complex and not fully understood but may involve recently discovered immune system changes. It has been demonstrated that periodontal inflammation is not only a local oral process but that periodontal microbial antigens can lead to activation of innate and adaptive immunity.[10] These activated cells of the immune system can contribute to developing pathology in the vessel wall and kidney, and penetrate the blood–brain barrier to influence the sympathetic nervous system.[29,30]

In a recent experimental model of hypertension, immunization of mice using *Porphyromonas gingivalis* antigens caused increased susceptibility to raised blood pressure in response to sub-pressor doses of angiotensin II.[31] Furthermore, in a recently reported clinical trial, analysis of pro- and anti-inflammatory cytokines and circulating cell immunophenotyping, has demonstrated significant reductions in circulating interferon-gamma, IL-17, IL-6 levels in plasma, as well as in immunosenescent CD28null CD57+ CD8+ T cells and activated CD8 + CD38 + T cells 2 months after intensive periodontal therapy.[10] This suggests that these cells may be linked to pathogenesis of PD, in addition to their known role in hypertension.

In summary, recent evidence has changed our understanding of the relationship between CV risk and PD. Initially thought to be observational and coincidental, it is now evident that periodontal health could be a key factor affecting vascular function, glucose control, metabolic health, and blood pressure. Considering the high prevalence of PD in the general population, targeting oral health may be an exciting new approach for reduction of both future CVD in the population as well as residual CV risk in patients.

References

References are available as supplementary material at *European Heart Journal* online.

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