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Unraveling the Link Between Periodontitis and Cardiovascular Disease

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This report of recent data from the Oral Infections and Vascular Disease Epidemiology Study (INVEST) study adds to an already substantial body of epidemiologic evidence for an association between cardiovascular disease (CVD) and periodontal disease.[1] Important questions regarding this association remain unanswered: What is the nature of the association? Does one disease influence the pathogenesis of the other? How might the association influence treatment strategies?

In what ways do Desvarieux and colleagues provide answers to any of these questions? They examine the relationship between longitudinal changes in intimal media thickness and changes over the same time period in periodontal disease severity, observing a correlation between the two. The report thus provides information about an as yet unexplored facet of the periodontitis-CVD association. Yet several factors mitigate the study's ability to answer the most important questions outlined above.

First, among the various measures of periodontal disease intensity, the authors focus attention on the "etiologic burden": the summed counts of 3 periodontitis-associated species divided by the summed counts of 11 species total, of which the "nonetiologic" species are possible periodontal pathogens or have been associated with a healthy periodontium. This confusing definition assumes that it is known exactly which bacteria cause periodontitis. However, the specific role of pathogens previously associated with periodontitis is not known. Indeed, the gram-negative bacteria of interest in this study have been strongly associated with periodontitis in cross-sectional studies, but longitudinal studies implicating these specific organisms as causative are lacking. In fact, evidence from several recent studies suggests that these pathogens emerge after initiation of the disease, possibly because the inflamed environment and tissue destruction provide an ecological niche for their overgrowth.[2,3] Thus it is potentially misleading to group them in an "etiologic burden" measure. Imbuing them with this meaning may even obscure their true relevance.

Second, as the authors point out, the experimental design precludes the assessment of the temporal relationship between periodontal disease and CVD because the 2 clinical aspects are shown only to covary over time. The chosen analysis therefore cannot discern among the following (or any other) possibilities: whether the observed association is likely to reflect a causal relationship in which periodontitis leads to CVD; whether it is due to a shared risk factor between periodontitis and CVD, such as host behaviors or immune responses; or whether it results from another source of confounding. If the association is causal, one possible explanatory mechanism is that specific periodontal pathogens directly influence the pathogenesis of cardiovascular lesions, presumably through direct interactions with the vessel wall. An alternative argument focuses on the inflammatory burden, which is now generally accepted as a major determinant in the pathogenesis of cardiovascular disease *and* periodontitis (for review, see Schenkein and Loos[4]). However, because very few inflammatory markers were included in the analysis, the work does little to distinguish between these 2 possibilities.

Animal experiments have allowed testing of hypotheses about whether periodontitis directly or indirectly influences the pathogenesis of cardiovascular lesions, and the resulting data support both mechanisms. Numerous reports implicate *Porphyromonas gingivalis* in the pathogenesis of CVD in mice (for review, see Reyes et al[5]), including evidence of direct invasion of vascular endothelium. An equally substantial literature demonstrates a role for periodontitis-induced inflammation. In a rabbit model of early atherogenesis, the presence of periodontitis significantly increased the extent of atherosclerotic lesions,[6] but no periodontal bacteria could be identified in the vessel wall lesions. A similar experiment in

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mice provided the same increase in atherosclerotic lesions, but in this case, periodontal pathogens were isolated from the lesion in the vessel wall.[7]

In humans as well, it is clear that increased inflammatory burden, such as that caused by metabolic syndrome or type-2 diabetes, is associated with increased risk for atherosclerosis.[8] The inflammatory burden of periodontitis is significant (for review, see Schenkein and Loos[4]), but it is not clear what role periodontal bacteria play in directly stimulating the inflammatory response in the vessel wall. Nevertheless, the plausibility of such a role was strengthened recently when viable *Porphyromonas gingivalis* were isolated from human atheromatous plaques.[9] Further prospective intervention studies that target inflammation and/or bacteria are required, and experimental design will be critical. For instance, interventions that reduce inflammation systemically, such as statins, do not clarify this question because successful interventions will improve both diseases simultaneously.[10] Rather, antibacterial or antiinflammatory treatment interventions must be applied locally to periodontitis-affected oral sites, with subsequent assessment of intermediate periodontal, bacterial, and immune markers as well as the degree of change in cardiovascular-related endpoints.

Periodontitis is recognized as an inflammatory disease of bacterial origin by the American Academy of Periodontology. Taken together, the data suggest that both in animals and humans periodontitis is also associated with the progression of atherosclerosis.[11] We applaud the authors' achievement in following a population-based cohort and making systematic measurements of both periodontal and CVD indicators over time, none of which are trivial undertakings. Their current report describes a novel way of examining the relationship between manifestations of periodontitis and CVD. Future work in the INVEST or other cohorts would benefit by including a greater number of time points and by incorporating assessment of an expanded number of bacterial taxa and host biomarkers. Such a systems biology approach may be needed to begin to tease out the complex relationship among these factors and between the 2 diseases. And ultimately, to distinguish among confounded or causal associations, intervention studies are likely to be needed.

Disclosures

None.

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