Association Between Nanobacteria and Periodontal Disease

To the Editor:

Hung et al.\(^1\) recently reported that the association between periodontal disease and incident tooth loss and peripheral arterial disease (PAD) is probably mediated via the oral infection-inflammation pathway. Discussions on the same hypothesis have been continuing for many decades. But so far, no clear cause-and-effect relationship has been found. Part of the link between these two diseases may be discovered through novel investigations of the opportunistic, infectious bacteria that colonize the mouth, form biofilm, cause periodontal disease, and activate white blood cells to release proinflammatory mediators that may contribute to heart disease and stroke. There are >300 species of known bacteria forming populations of several hundred billion in the human oral cavity. The number of bacteria reaches a thousand billion when the mouth is not sufficiently cleaned.

Coronary atherosclerosis (CA) has been suggested to be an inflammatory disease in which chronic dental infections may trigger pathogenic mechanisms in the walls of arteries. Vascular calcification increases the severity of CA and is one of the biggest problems in this disease. Definitive mechanisms causing vascular calcification are unknown. Because nanobacteria (NB) form surface calcifications at physiological levels of calcium and phosphate, they have been hypothesized to mediate tissue calcifications.\(^2\) These self-replicating, biofilm-forming, tetracycline-sensitive\(^3\) agents remain controversial because of apatite coat and resistance to extraction of their components by conventional methods.\(^2\) Our preliminary work with 18 dental pulp stones, selected only by severity of the stone formation, indicated the presence of NB antigens in the demineralized stones.\(^4\) Furthermore, we found a high incidence of kidney stones and gallstones in the patient group and in their parents.\(^4\) A research group from the Mayo Clinic in Rochester, Minn, has recently detected NB in calcified carotid arteries, aortic aneurysms, and cardiac valves by using electron microscopy and immunohistochchemical staining techniques.\(^5\)

Should the link between oral disease and heart disease be firmly established, future studies should focus on identifying the specific biological factors involved and transferring this knowledge to prevent disease. The model for modern infectious disease research is to systematically consider a variety of potential infectious agents. Because NB can be identified by using culture, monoclonal antibodies, and electron microscopy techniques, and because they were detected in both dental pulp stones and CA, NB should be considered a potential causative agent to be screened in related diseases. We propose that NB may provide a potential bridge between periodontal diseases and PAD. This relationship is worthy of further study.

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Response

We have proposed several potential explanations for the association between oral health and cardiovascular disease, and the activation or release of inflammatory mediators caused by bacteria is one.\(^1\)–\(^3\) However, different measures of oral health, such as the number of remaining teeth, recent tooth loss, and periodontal disease that could reflect different pathways, showed different relationships with the following atherosclerotic diseases: coronary heart disease, stroke, and peripheral arterial disease.\(^1\)–\(^3\) This suggests that the association between oral health and cardiovascular diseases is complex.

Antibiotics consistently reduced atherosclerotic vascular disease in four of five small clinical trials with low power, but larger trials testing the relationship between antibiotics and coronary heart disease gave equivocal results.\(^4\) A possible explanation consistent with these data may be that infection plays a larger role in atherosclerotic disease such as peripheral arterial disease compared with coronary heart disease, where other factors such as plaque stability may be more important. We therefore agree with Çiftçioglu et al that >300 species of known bacteria with populations of several hundred billion in the human oral cavity, and even higher among periodontal disease patients, could possibly contribute to development of peripheral arterial disease in particular. Nanobacteria (NB) might be associated with tissue calcifications and hence could increase risk of coronary atherosclerosis. Although NB has been detected in calcified carotid arteries, the evidence to support a causal association with cardiovascular diseases is still limited. Moreover, there is no evidence that NB is associated with periodontal diseases, even though NB has been identified in tooth pulp stone and saliva, as well as in dental plaque.\(^5\)

We agree that it is important to evaluate specific biological factors that could contribute to these associations, including common genetic factors, microbial factors, cytokines, and other inflammatory mediators. Microorganisms, including bacterial species known to be associated with periodontal disease, are definitely worthy of further study in this context. The qualitative or quantitative differences of NB in specimens from the oral cavity (ie, saliva, dental plaque, or gingival crevicular fluid) between subjects with and without periodontal disease must be documented while considering the role of NB in the relationship between periodontal disease and peripheral artery disease, and we agree that this is worthy of further study.

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