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Childhood oral infections and subclinical atherosclerosis in adulthood: Should we wait for causality or just treat?

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Should We Wait for Causality or Just Treat?

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Pussinen et al[1] reported that the presence of oral infections in childhood was associated with an increased risk of subclinical atherosclerosis in adulthood in a cohort of 755 individuals observed from 1980 to 2007. There are 3 possible explanations for this observation. First, individuals who have poor oral health as children also have poor oral health as adults.[2] Studies conducted among adults support the hypothesis that poor oral health leads to atherosclerosis. Chronic oral infections induce low-grade local and systemic inflammation that is hypothesized to mediate atherosclerosis.[3] Microorganisms associated with periodontal disease have been isolated from atherosclerotic lesions. Poor oral health is also associated with a higher risk of atherosclerosis and cardiovascular disease (CVD) in high-quality prospective studies conducted among many different populations.[4] In observational studies, long-term periodontal care has been shown to be associated with improved glycemic control among patients with type 2 diabetes.[5] In randomized clinical trials, periodontal treatment has been shown to reduce inflammation and favorably affect blood pressure, serum lipid levels, and endothelial function.[6] Despite this convincing preliminary evidence suggesting that periodontal treatment has a beneficial effect on CVD, to our knowledge there are no reports in the literature of a clinical trial testing this hypothesis. This is probably because periodontal disease is not cured but rather controlled or contained by regular dental treatment. Periodontal disease begins as a painless, low-grade infection of the gums, with the deposit of dental plaque that gradually calcifies, causing the progressive destruction of the supporting structures of the teeth. Early periodontal disease may not have any symptoms and is usually diagnosed by the dentist. Initial treatment typically consists of mechanical debridement to remove calcified plaque and instructing the patient to maintain good oral care and recalling the patient for an assessment 3 to 6 months later. At the recall visit, the dentist reassesses and decides on next steps. Conducting a clinical trial with this protocol is challenging. A conventional randomized clinical trial is feasible if the outcome can be observed within 3 to 6 months (such as for inflammatory markers, serum lipid levels, blood pressure, and endothelial function). Because CVD takes several years to develop, conducting a clinical trial is not feasible; even if periodontal treatment is randomly assigned at the outset, subsequent treatment is not random. Therefore, the question of the effect of periodontal disease on CVD remains unresolved.

The second possible explanation for the findings Pussinen et al[1] reported is that poor oral health does not have a causal effect on CVD. Rather, poor cardiovascular and oral health share common risk factors, such as smoking, poor diet, physical inactivity, or unknown genetic factors predisposing individuals to a hyperinflammatory response. If some of these risk factors were poorly measured, unmeasured, or unknown, periodontal disease and CVD would be associated owing to confounding, but treating periodontal disease would not affect CVD risk. To account for confounding, Pussinen et al[1] took the following approach. Because information was not available for genetic, lifestyle, and behavioral risk factors, they adjusted for the following downstream risk factors: body mass index, blood pressure, serum lipid levels, hyperglycemia, and C-reactive protein level. These downstream risk factors were measured up to 5 times during follow-up and summarized using the area under the curve method to get measures of cumulative exposure over follow-up, which were used for

adjustment in multivariable models. Because most genetic, behavioral, and lifestyle factors exert their effect on CVD risk through these downstream factors, controlling for them in the analyses with the area under the curve method was an effective strategy to control for the average effect of potential confounders over follow-up and to minimize bias. Finally, E values ranged from 3.31 for the whole population to 3.93 for boys. This implies that an unmeasured confounder would need to have a relative risk of 3.31 or greater for the exposure and the outcome to explain the results.[7] Therefore, unmeasured confounding is not a likely explanation for these results.

The third possible explanation is that the positive association observed between poor oral health in childhood and atherosclerosis in adulthood was because of selection bias secondary to loss of follow-up. Selection bias occurs in cohort studies when there is informative loss to follow-up. For selection bias to explain the observed results, 1 or both of the following 2 groups of people would need to selectively drop out of the study: those with poor oral health as children and no atherosclerosis as adults or those with good oral health as children and atherosclerosis as adults. This is implausible because atherosclerosis was subclinical. Moreover, the investigators corrected for selection bias using inverse probability weighting, and the association persisted.

The results of the observational study by Pussinen at al[1] suggest that childhood infections of the oral cavity may increase CVD risk in adulthood. Even if the question of causality remains unanswered, with issues pertaining to the performance of a conventional randomized clinical trial in this context, the article by Pussinen et al[1] underscores the idea that the distinction between oral health and systemic health is blurred and somewhat artificial. Cardiovascular disease and periodontal disease share common risk factors, and controlling those risk factors could result in better overall health. For example, if dentists encouraged their patients to quit smoking and visit their primary care clinician, and primary care clinicians encouraged their patients to maintain good oral health and visit their dentist regularly, the ultimate benefit would be better dental and cardiovascular health.

ARTICLE INFORMATION

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