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Review Article

Current evidence and biological plausibility linking periodontitis to atherosclerotic cardiovascular disease

Koichi Tabeta DDS,PhD[a,*], Hiromasa Yoshie DDS,PhD[a], Kazuhisa Yamazaki DDS,PhD[b]

[a] *Division of Periodontology, Department of Oral Biological Science, Niigata University Graduate School of Medical and Dental Sciences, Japan*
[b] *Laboratory of Periodontology and Immunology, Division of Oral Science for Health Promotion, Niigata University Graduate School of Medical and Dental Sciences, Japan*

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Summary The relationship between poor oral health and systemic diseases has been increasingly recognized over the past two decades. Atherosclerosis is an important basal component of atherosclerotic cardiovascular disease (ACVD), which is the *primary* cause of death worldwide, including Japan.

The accumulation of multiple individual epidemiological studies has paved the way for subsequent systematic reviews that have demonstrated that periodontitis can be considered as an emerging risk factor for ACVD. Although the causal mechanisms by which periodontitis accelerates ACVD have not been fully elucidated, plausible evidence regarding the inflammatory response due to inflammatory mediators and bacterial etiologies, and the recognition of altered lipid metabolism in patients with periodontitis suggest that infection with periodontopathic bacteria can influence atherogenesis *in vitro* and *in vivo*. Animal model studies have strengthened this evidence. However, there have been a lack of interventional studies that show the effects of periodontal treatment on the future risk of ACVD; this lack of evidence critically weakens the importance of the relationship between the two diseases. This review presents a summary of the current evidence and biological plausibility that link periodontitis to ACVD.

* Corresponding author at: Division of Periodontology, Department of Oral Biological Science, Niigata University Graduate School of Medical and Dental Sciences, 2-5274 Gakko-cho, Chuo-ku, Niigata 951-8514, Japan. Tel.: +81 25 227 0744; fax: +81 25 227 0744.
E-mail addresses: koichi@dent.niigata-u.ac.jp, tabeta@dent.niigata-u.ac.jp (K. Tabeta).

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1. Introduction

Periodontitis is caused by infection with a group of bacteria, primarily Gram negative and anaerobic species. The inflammation triggered by a bacterial infection is characterized by mononuclear cell infiltration into the gingival tissues, leading to connective tissue destruction and alveolar bone resorption. The loss of tooth function caused by periodontal destruction diminishes masticatory function and impairs facial configuration. Furthermore, periodontitis is a major public health issue because it can be a source of social inequality, decreases quality of life, and increases dental costs; it also has a potential impact on systemic diseases.

Individual epidemiological studies and subsequent systematic reviews have demonstrated that periodontitis can be considered as an emerging risk factor for atherosclerotic vascular disease (ACVD) [1]. Although the causal mechanisms by which periodontitis accelerates ACVD have not been fully elucidated, plausible evidence regarding the inflammatory response due to inflammatory mediators and bacterial etiologies, and the recognition of altered lipid metabolism in patients with periodontitis suggest that infection with periodontopathic bacteria can influence atherogenesis (Fig. 1). Several studies conducted *in vitro* and using animal models have demonstrated some causal mechanisms in human patients with periodontitis; these mechanisms suggest that infection and the subsequent inflammatory response may be a key to elucidating the association between atherosclerosis and periodontitis. This review presents a summary of recent studies on the relationship between periodontitis and ACVD.

2. Epidemiological evidence

The association between poor oral health and ACVD has been increasingly recognized over the past two decades. A significant number of groups have conducted epidemiological studies, and the findings have been systematically reviewed several times [1—6]. A comprehensive review by an American Heart Association (AHA) working group concluded that periodontal disease is associated with atherosclerotic vascular disease independent of known confounders [7,8]. However, the working group further concluded that there was no evidence of a causal link. This review further pointed out gaps in the published research and methodological issues that should be improved in future research, such as the need for uniform criteria for the evaluation and case definitions of periodontitis. It further emphasized the need for well-designed, controlled interventional studies with standard treatment protocols as well as considerations for issues such as sustainability of treatment response over time [7,8]. To this point, Dietrich et al. [9] systematically reviewed cohort and case—control studies while minimizing the effects of misclassification by including studies that evaluated periodontal probing depth/clinical attachment loss and/or radiographically assessed alveolar bone loss. The researchers observed that the association was stronger in younger adults and that there was no evidence for an association between periodontitis and the incidence of coronary heart disease (CHD) in subjects aged >65 years. The conclusions from this review were that the evidence for an increased risk of ACVD in patients with periodontitis compared with that in patients without the disease only applied to a limited section of the population [9]. Thus, the clinical parameters of periodontitis, such as periodontal probing depth, clinical attachment loss, and/or radiographic assessment of bone loss, have all been associated with an increased risk of ACVD independent of established risk factors. However, the amount of excess risk adjusted for ACVD risk factors varied across studies according to the type of cardiovascular outcome and age and sex of the subjects. Specifically, the risk has been greater in males and younger individuals [9—12].

3. Biological plausibility

3.1. Inflammatory mediators

Atherosclerosis, an inflammatory disease, is the major cause of ACVD and is initiated by injury to the vascular endothelium [13—16]. It is a major cause of diseases that involve plaque formation, plaque disruption, and subsequent atherothrombosis [14,17]. Although the accumulation of atheromatous