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Review

Links between atherosclerotic and periodontal disease

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ABSTRACT

Periodontal disease (PD) and cardiovascular disease (CVD) are highly prevalent in the modern community. Both pathologies are chronic inflammatory disorders, which are influenced by multiple risk factors. In part, these factors such as age, smoking, and diabetes overlap between PD and CVD. Epidemiological studies suggest that PD is strongly associated with increased CVD risk. Biochemical and physiological analyses involving in vitro experiments, animal models, and clinical studies provided evidence for the substantial impact of periodontal pathogens, their virulence factors, and bacterial endotoxins on all general pathogenic CVD mechanisms such as endothelial dysfunction, systemic inflammation, oxidative stress, foam cell formation, lipid accumulation, vascular remodeling, and atherothrombosis. Interventional studies showed moderate beneficial effects of PD treatment on reducing systemic inflammation and endothelial dysfunction. However, no interventional studies were performed to assess whether periodontal therapy can primarily prevent CVD. In summary, current data suggest for a strong contributory role of periodontal infection to CVD but cannot provide sufficient evidence for a role of PD as a cause for cardiovascular pathology.

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1. Introduction

Teeth are surrounded by gingival tissue. Between the tooth and gingival tissue, a space (termed gingival sulcus) can occur. The gingival sulcus is lined by sulcular epithelium that joins with the oral cavity epithelium at the top of the gingival margin. In the gingival sulcus, the epithelium and crown enamel form unique surfaces colonized by oral bacteria. In this microenvironment, bacteria form a biofilm called dental plaque.

Primary colonizers, which populate the gingival sulcus, involve streptococci (such as *Streptococcus oralis*, *Streptococcus mutans*, and *Streptococcus sanguis*), Neisseria sp., etc. These anaerobic bacteria greatly decrease local availability of oxygen thereby providing an option for obligate anaerobes to populate and grow in the gingival sulcus. In the dental plaque, primary colonizers provide substrates and form a background for attachment of secondary colonizers (that are predominantly anaerobic) such as actinomycetes (*Actinomyces odontolyticus* and *Actinomyces naeslundii*), *Fusobacterium nucleatum*, Veillonella sp., etc. (Rickard et al., 2003). Overall, the dental plaque microflora exceeds 500 species (Moore and Moore, 1994).

In the dental plaque, bacterial composition is influenced by many factors including supply with oxygen, pH, diet, oral hygiene, and interactions between microbes.

Above and below the gingival margin, bacterial composition significantly differs. In healthy individuals, subgingival flora is mainly composed by aerobic streptococci, anaerobic actinomycetes, and *F. nucleatum* (Moore and Moore, 1994). Poor oral hygiene, insufficient or lacking dental care, smoking, altered immunity, and other harmful factors could induce gingivitis (i.e. inflammation of gum tissue). Subgingival plaque could play a major role in the development of gingivitis.

In gingivitis, numbers of subgingival plaque microorganisms greatly increase along with the enrichment of the subgingival plaque microflora with Gram-negative obligate anaerobes (Moore et al., 1987) including *Porphyromonas gingivalis* (Socransky et al., 1991), *Aggregatibacter actinomycetemcomitans* (Zambon et al., 1983), *Prevotella intermedia* (Yang et al., 2014), *Prevotella melaninogenica* (Mandell et al., 1992), *Tannerella forsythensis* (Yang et al., 2004), *Fusobacterium periodontium* (Kobayashi et al., 2008), and *Campylobacter rectus* (Gmür et al., 2004). All these bacteria and some other microbes are pathogens involved in gingivitis and periodontitis.

In the subgingival plaque, bacteria form complex relations between each other and host cells. Plaque microbes are embedded into the extracellular matrix (ECM) of the sulcular epithelium (Gibbons, 1989). Periodontopathogens such as *P. gingivalis* and *A. actinomycetemcomitans* invade epithelial cells via the mechanism of endocytosis (Meyer et al., 1996). In the host cells, bacteria amplify and spread through intercellular protrusions to other cells (Andrian et al., 2006). The bacterial invasion is accompanied by release of pro-inflammatory mediators that attract proinflammatory immune cells to the gingival sulcus (Jotwani et al., 2001). Periodontal pathogens exhibit marked adaptation capacity that supports survival within the invaded cells, neutralization of immune cells, inactivation of anti-microbial factors, and induction of host mechanisms leading to tissue degradation (Amano, 2007).

The deepening of the gingival sulcus caused by dental plaque growth, local inflammation, and bacterially mediated destruction of the gingival fiber attachment leads to the formation of the periodontal pocket. The periodontal pocket is a preferable site for accumulation of periodontal pathogens where they aggravate inflammation of surrounding tissues and could stimulate progression of gingivitis to periodontal disease (PD) (Smalley, 1994). In PD, the connective tissue attachment is lacking and the dental plaque expands apically along the root tissue causing progressive loss of the alveolar bone around the tooth and finally loss of the tooth itself. In periodontitis, the periodontal pocket releases gingival crevicular fluid (GCF), an inflammatory exudate containing cell debris, bacterial degradation products, inflammatory mediators, connective tissue fragments, enzymes, and other proteins (Subrahmanyam and Sangeetha, 2003). Inflamed periodontal tissue is frequently or persistently bleeding providing an option for periodontal infection to enter the bloodstream.

Indeed, oral pathogenic bacteria and their endotoxins could disseminate into the systemic circulation via gingival injuries and affect distant organs (Hirschfeld and Kawai, 2015). Oral commensals may represent a serious risk for individuals with predisposive cardiac alterations (heart valve disease, pacemaker implantation, and so on) and cause infective endocarditis (Ito, 2006). First evidence for positive association between the poor dental health and myocardial infarction (MI) (Mattila et al., 1989) initiated a wave of interest to study possible relations between dental infections and cardiovascular diseases (CVD) including atherosclerosis. Despite for heterogeneity of the studies, overall results of epidemiological studies suggest for a modest but significant association between periodontal infections and CVD that is independent on the effects of confounders (Kebschull et al., 2010). Experiments in animal models and in vitro studies found potential molecular mechanisms linking PD and atherosclerosis.

2. Epidemiological studies

Findings from the major epidemiologic studies involving thousands of individuals were comprehensively discussed in recent reviews (Kebschull et al., 2010; Lockhart et al., 2012). Several meta-analyses were performed and a positive association between PD and cardiovascular disease (CVD) was reported. Blaizot et al. (2009) showed that PD patients have increased risk of developing CVD (odds ratio (OR), 2.35 (95% confidence interval (CI): 1.87; 2.96), $p < 0.0001$) and relative risk (RR), 1.34 (95% CI: 1.27; 1.42), $p < 0.0001$). Sfyroeras et al. (2012) found association between PD and ischemic stroke reporting that PD subjects have 1.47-fold and 2.63-fold adjusted risk to develop stroke in prospective and retrospective studies respectively. In a recent meta-analysis, Orlandi et al. (2014) observed significant association of periodontitis with increased carotid intima-media thickness (cIMT; a characteristic of carotid atherosclerosis) and impaired flow-mediated dilatation (FMD; a characteristic of endothelial dysfunction).

Smoking is a strong confounding factor that significantly influences apparent association between PD and CVD (Hujoel et al., 2002). Current multivariate analyses include adjustments for several smoking-related variables such as smoking status, a quantity of pack-years, a time after cessation, second-hand smoking, etc. (Nasry et al., 2006; Costa et al., 2013). Indeed, correction for several smoking-related confounders strengthens the validity of observed association between PD and CVD. In addition, strong association between periodontitis and CVD was repeatedly shown in never-smokers (Okoro et al., 2005; Pussinen et al., 2007; Sim et al., 2008). These findings in turn indicate that peridontitis represents an independent cardiovascular risk factor.

Association between PD and CVD is influenced by age, with stronger association in younger patients aged <60–65 years. compared with those who is older 60–65 (Demmer and Desvarieux, 2006; Dietrich et al., 2008; Sim et al., 2008; Jimenez et al., 2009). The age-dependent association between two diseases may not be the only a result of effect modification when the observed relationship is caused by interaction between two or more risk factors (Ylöstalo and Knuuttila, 2006). The independent influence of age on PD-CVD association could be supported by data of Dietrich et al. (2008) who started the follow-up study in the 1960s, i.e. significantly earlier when PD-CVD association was first reported. Indeed, this finding is not a false post hoc observation.

Recently, in a large-scale retrospective cohort study, Chou et al. (2015) reported that patients with treated severe periodontitis aged >60 years. have increased risk of long-term major adverse cardiovascular events compared with younger subjects (<60 years). The association remained after adjustment for other potential CVD-related confounders such as gender, hyperlipidemia, hypertension, and diabetes. This finding