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Review

Interaction between periodontal disease and atherosclerotic vascular disease – Fact or fiction?

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ABSTRACT

C-reactive protein (CRP) level is associated with the 10-year risk of an atherosclerotic vascular disease (ASVD), suggesting presence of systemic inflammation probably long before ASVD is present. Where, however, does this systemic inflammation come from? One active area of research has been the study of dental infection and various forms of periodontal disease (PD), both of which are highly prevalent in populations at risk for ASVD. Recent data show that ASVD and PD interact with each other via systemic release of specific pro- and anti-inflammatory cytokines, small signal molecules and enzymes which modulate initiation and progression of the chronic inflammatory reaction involved in both diseases. In addition, periodontal pathogens were identified within atherosclerotic lesions and thrombi isolated from myocardial infarction patients. LDL cholesterol, a strong risk factor for ASVD, is also associated with PD; and statins, used to treat ASVD, are also active to prevent or reduce PD. Finally, there is growing evidence for common genetic susceptibility factors involved in both diseases. These findings support commonalities with respect to the pathogenic mechanisms involved in both inflammatory diseases. Conversely, a causative relationship cannot yet be concluded in the absence of data from large longitudinal cohort and randomized controlled intervention trials.

1. Introduction

Periodontal disease (PD) is a highly prevalent chronic inflammatory disease affecting the tooth-supporting structures [1], and atherosclerotic vascular disease (ASVD) is a highly prevalent chronic inflammatory condition affecting arterial blood vessels [2,3]. ASVD is the leading cause of morbidity and mortality in industrialized countries and is among the major causes of death worldwide [4]. In the US, ASVD accounts for about 40% of all deaths each year; over 700,000 people die each year from ASVD (the vast majority from heart disease and stroke) [5]. ASVD includes “hard” or major events, like coronary death, myocardial infarction (MI), death due to cerebrovascular disease and stroke, as well as “soft” outcomes, such as angina pectoris, revascularization and peripheral vascular disease, which are not so life threatening [2]. The traditional risk factors for ASVD have been established based on large prospective cohort studies. Widely used risk scores for general cardiovascular events (*i.e.* the Framingham and the PROCAM risk scores) encompass variations of the following sex-specific predictors: age, diabetes, smoking, treated and untreated systolic blood pressure, total cholesterol, high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides and body mass index (BMI) replacing triglycerides in simpler models, and family history of a major ASVD event (PROCAM) [6,7].

However, these factors explain only about half of all deaths from ASVD, and almost half of all hard ASVD events occur in patients without the classic risk factors [7,8]. For instance, about 40% of CHD deaths occur in people with cholesterol levels that are lower than the population mean [6,7]. Therefore, identifying additional, so-called emerging risk factors, which are non-traditional, but may play major roles in explaining some of the variability in ASVD risk is a core area of current medical research. In this context, the hypothesis that dental infection plays an important role as risk factor acting independently of the classic Framingham risk factors is attractive.

Periodontal diseases are an entity of localized, inflammatory

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diseases affecting the epithelial, connective and osseous tissues surrounding the teeth [9]. According to the most common classification scheme, introduced by the International Workshop for a classification of Periodontal Diseases and Conditions in 1999 [10], eight main subtypes are discriminated. Bacteria once attached to teeth along the gingival margin grow within minutes to form biofilms and induce an immune response in the adjacent gingival tissues. After a few days, clinical abnormalities develop consisting of swelling, redness and bleeding [11]. If the bacterial biofilm and accompanying inflammatory reaction migrates apically along the root surface and affects the tooth supporting structures the gingival inflammation becomes periodontitis [12]. It is estimated that in most non-clinical populations 5–20% of the subjects suffer from severe, generalized periodontitis [13,14]. The World Health Organization estimates that advanced disease stages with periodontal pockets ≥6 mm affects 10–15% of all adults around the world [15].

Could oral infectious agents promote atherogenesis? Considering the existing diversity of supporting and contradicting evidence, answering this question convincingly and beyond any doubt seems difficult. Since a better understanding of the relationships existing between oral infections and atherosclerosis would have profound implications for risk stratification, disease prevention and treatment, we considered that it might be of interest to review the current status of knowledge and discuss some ongoing and future directions of research in this area. In 2012, Lockhart et al. issued a scientific statement for the American Heart Association covering the topic [16]. The most notable conclusions then were: (1) although observational studies supported an association between PD and ASVD independent of known confounders, a causative relationship existing between the two diseases could neither be supported nor dismissed, and (2) it was unclear whether periodontal interventions could prevent ASVD or modify its outcomes in the long-term [16]. Since then, many additional studies have been conducted and results published. Thus, the scope of the present review is to focus on potential progress obtained by new work published after 2012.

1.1. Oral infections and atherosclerosis

Past research showed that atherosclerosis is the result of a chronic inflammatory process and inflammation is seen to play a pivotal role in all phases of atherogenesis [recently reviewed in Ref. [17]]. From a basic perspective, specific cytokines, receptors, enzymes and adhesion molecules which participate in adaptive and innate immunity promote the recruitment of monocytes to the arterial wall, followed by foam cell formation, cellular proliferation of the intima, wall thickening, and ultimately arterial narrowing. Finally, rupture of the mature plaque can lead to acute luminal occlusion resulting in a major ASVD event with devastating consequences for the affected organs. From an epidemiologic perspective, a wealth of evidence demonstrates that biomarkers of inflammation are increased among apparently healthy men and women at risk for future ASVD even when cholesterol levels are low. The magnitude of the effect is similar as that of other well established risk factors, such as hypertension, overweight and hypercholesterolemia [18]. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial, a randomized placebo-controlled trial including ~18,000 patients demonstrated that statin therapy reduced risk of myocardial infarction and stroke by more than 40% in individuals with low cholesterol who had increased levels of C-reactive protein (CRP) [19]. CRP is a pattern recognition molecule, which participates in the systemic response to inflammation [20]. The protein binds to specific molecular configurations that are typically exposed during cell death or are found on the surfaces of pathogens [21]. It is a sensitive non-specific acute-phase marker for infection and inflammation regulated by cytokines interleukin-6 (IL-6), interleukin-1β (IL-1β) and tumor necrosis factor-α (TNF-α) [22].

Based largely on the JUPITER trial, it was suggested that it might be useful to include CRP and other soluble biomarkers of inflammation in risk prediction of first cardiovascular events, particularly in individuals who have low cholesterol levels and thus are mostly at intermediate risk for ASVD according to standard risk scores [23–28]. In 2012, the Emerging Risk Factors Collaboration presented data showing improvements in the prediction of a first ASVD event when the concentration of circulating CRP was added as additional risk factor to standard risk scores [18]. From the presently available evidence it can be concluded that oral infections including gingivitis and chronic and aggressive periodontitis consistently elevate systemic levels of CRP. One of the earliest studies was conducted by Boucher et al. [29], who demonstrated that the highest incidence of positive CRP tests and the strongest CRP test reactions were present in patients with acute alveolar abscesses. Subsequently, various studies showed that patients with less severe PD such as chronic periodontitis also have increased serum levels of CRP relative to unaffected subjects [30–33]. The level of infection with periodontal pathogens is positively correlated with CRP level [34,35], and the extent of CRP elevation seems to be pathogen-specific: *Porphyromonas gingivalis* induces pronounced CRP increases whereas *Aggregatibacter actinomycetecomitans* is less active [35,36].

It is conceivable that systemically elevated CRP, accompanied by increases of other inflammatory mediators, may increase inflammatory activity in existing atherosclerotic lesions, thereby increasing the risk of an ASVD event (Table 1). Chen et al. [37] showed that platelet-activating factor (PAF), a potent pro-inflammatory mediator, was almost fivefold elevated in serum from patients with PD compared with healthy controls. Patients who had only PD or only CHD and those who had CHD together with PD all showed similarly elevated PAF levels, indicating that one of the two conditions is sufficient to fully release the PAF response. This observation together with the fact that PD usually has an earlier onset than ASVD suggests that systemic PD-induced PAF elevations may play a pro-inflammatory role early on in atherogenesis rather than in the later steps, which are typically involved in CHD. Likewise, presence of CHD may have a stimulatory effect on the course of PD via CHD-mediated PAF elevations. This and a number of other studies support that ASVD and PD do in fact have a two-way relationship by interacting with each other via systemic release of specific pro- and anti-inflammatory cytokines, small signal molecules, such as eicosanoid inflammatory mediators and shingosine-1-phosphate (S1P), and enzymes which modulate initiation and progression of the chronic inflammatory reaction involved in both diseases (Fig. 1).

1.2. Two-way relationship – potential mechanisms

Infections of remote origin may initiate and promote systemic inflammatory reactions by several mechanisms, all of which have been verified in animal or human studies. These mechanisms include (A) the local production of inflammatory mediators in inflamed gingival or periodontal tissues elevating the systemic inflammatory burden and (B) the release of pathogenic bacteria from periodontal affected tissues into the vascular system, either by direct release into the circulation or as internalized particles of immune cells via the lymphatic or blood system. Over the last decades isolated steps of these pathways or singular experimental components have been investigated mostly in animal models, however, the entire mechanisms have not been