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Review Article

Interrelationships of Periodontal Disease, Systemic Inflammation, and Cardiovascular Disease

Simone Taylor S and Hennekens CH

Charles E. Schmidt College of Medicine, Florida Atlantic University, USA

Abstract

In United States (US) adults, periodontal disease is the most common dental condition and, worldwide, is also one of the most common chronic inflammatory diseases affecting a majority of the population. Bacteria in the plaque seem to be the initial cause of periodontal disease. This triggers an inflammatory response where inflammatory mediators and local oral bacteria in people with periodontitis will eventually enter the systemic circulation. These, in turn, will stimulate the liver to produce acute phase proteins which are biomarkers of the systemic inflammatory response (3).

High sensitivity C-reactive protein (hsCRP) is an acute phase protein that it produced and released by the liver in response to inflammation. HsCRP levels elevate with systemic inflammation and tend to remain stable over time. Further, hsCRP is an accurate measure of systemic inflammation and a sensitive marker for cardiovascular disease (CVD).

The hypothesis that decreasing inflammation reduces risks of cardiovascular disease is strongly supported by the results of the Justification for the Use of Statins in Primary Prevention: Intervention Trial Evaluating Rosuvastatin (JUPITER) trial as well as the Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS). All these findings provide support for the hypothesis that reduction of dental plaque in patients with periodontal disease will decrease inflammation as measured by hsCRP. As hsCRP is an accurate measure of inflammation and sensitive marker of CVD it is also plausible to hypothesize that reduction of dental plaque in patients with periodontal disease will decrease in risks of CVD. The direct test of this hypothesis requires a large scale randomized trial of sufficient size and duration designed a priori to do so. Such a finding would have major clinical and public health implications.

Keywords: Periodontal disease, Systemic inflammation, Cardiovascular disease

Introduction

In the early part of the 7th century, the Assyrians hypothesized a link between oral and systemic diseases.Specifically, they proposed that oral health can affect the overall health of the body [1]. In recent years, systemic inflammation has been proposed as a plausible mechanism to explain any valid statistical association between periodontal disease and Cardiovascular Disease (CVD).The effect size, however, is likely to be small and case-control and cohort studies have inherent confounding by age, gender, socioeconomic status, obesity and perhaps other unknown confounders that may be as large as the effect size.Thus, the most reliable design strategy to test the hypothesis is a randomized trial of sufficient size and duration [2]. In this manuscript, we summarize the available totality of evidence on periodontal disease, systemic inflammation, and CVD.

Periodontal Disease

In United States (US) adults, periodontal disease is the most common dental condition in and, worldwide, is also one of the most common chronic inflammatory diseases affecting a majority of the population [3]. In the US 47% of adults over the age of 30 have some form of periodontal disease. Periodontal disease can be defined as the destruction of the tooth and its supporting structures including the gingiva (gums), periodontal ligament, and alveolar bone due to infection.

Periodontal disease can lead to systemic inflammation via the spread of oral bacteria and or its products. Oral bacteria can enter the bloodstream through gingival pockets that are ulcerated and diseased. The binding of oral bacteria (that survives in the bloodstream) to various sites within the body, results in systemic inflammation. On a cellular level, when endothelial cells and leukocytes recognize bacterial antigens in the bloodstream, the pro-inflammatory mediators CRP and prostaglandin are secreted. Cells of the immune system continue to produce more inflammatory cytokines that are typically associated with osteoclast genesis and tissue destruction. The high level of pro-inflammatory cytokines ultimately leads to systemic inflammation. In summary, bacteria in the plaque seem to be the initial cause of periodontal disease.This triggers an inflammatory response where inflammatory mediators and local oral bacteria in patients with periodontitis will eventually enter the systemic circulation.These, in turn, will stimulate the liver to produce acute phase proteins which are biomarkers of the systemic inflammatory response [4,5].

Inflammatory Biomarkers:The role of high sensitivity C - reactive protein

High sensitivity C-reactive protein (CRP) is an acute phase protein that is produced and released by the liver in response to inflammation. Basic research has suggested plausible mechanisms to explain why CRP is a sensitive marker for systemic inflammation. promotes recruitment of monocytes into atheromatous plaque and induces endothelial dysfunction via nitric oxide suppression. In addition, CRP also increases the expression of adhesion molecules such as plasminogen activator-1 which have been hypothesized to play a role in the development of CVD. Finally, CRP levels elevate as inflammation increases in the body and remain stable over a long time.CRP is an accurate measure of systemic inflammation [6].

In the Physicians Health Study, a randomized, double-blind, placebo-controlled trial of aspirin in the primary prevention of CVD, CRP was measured in plasma C-reactive protein, a marker for systemic inflammation, in 543 apparently healthy men at baseline who subsequently developed MI, stroke, or venous thrombosis and an equal

***Corresponding author:** Charles H. Hennekens, Charles E. Schmidt College of Medicine, Florida Atlantic University, USA

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number of controls who did not report vascular disease during a follow-up period exceeding eight years. Subjects were randomly assigned to receive aspirin or placebo at the beginning of the trial. At baseline, CRP levels were significantly higher among men who subsequently developed MI (1.51 vs. 1.13 mg per liter, P<0.001) or ischemic stroke (1.38 vs. 1.13 mg per liter, P = 0.02), but not venous thrombosis (1.26 vs. 1.13 mg per liter, P = 0.34), than among those who did not develop subsequent vascular events. The men in the quartile with the highest CRP levels had about three times the risk of MI (relative risk, 2.9; P<0.001) and two times the risk of ischemic stroke (relative risk, 1.9; P = 0.02) than those in the lowest quartile. Risks were stable over long periods, were not modified by smoking, and were independent of other lipid-related and non–lipid-related risk factors. In these analyses, aspirin was associated with significant reductions in the risk of MI (55.7 percent reduction, P = 0.02) among men in the highest quartile but with only small, non significant reductions among those in the lowest quartile (13.9 percent, P = 0.77) of CRP.Thus, the baseline concentrations of CRP predicted risks of future MI and stroke.Moreover, the reduction associated with the use of aspirin in the risk of a first MI appeared to be directly related to the level of CRP.These findings indicated that CRP is a sensitive marker for future CVD and contributed to the formulation of the hypothesis that anti-inflammatory agents reduce risks of CVD [7].

The American Heart Association and Centers for Disease Control and Prevention have defined risk groups based on CRP as low: <1.0 milligram per liter (mg/L); average: 1.0 to 3.0; and high: > 3.0.In addition, values above 10.0 areexcluded because they are due to other systemic causes of inflammation such as pneumonia, burns, and even some cancers [8].

Cardiovascular Disease

CVD includes principally nonfatal MI, stroke, and cardiovascular death and remains the leading cause of mortality in the United States since the 1950's and is becoming so worldwide. The World Health Organization (WHO) estimates that, in 2015, CVD was responsible for the deaths of 17.7 million people [9].While death is inevitable, premature death is not and the systemic inflammatory response associated with periodontal disease may represent a potentially avoidable cause of premature death due to CVD.

In a randomized trial of 246 participants with periodontal disease and CVD, 161 were randomized to non-surgical periodontal treatment therapy that included scaling (the removal of bacteria from the root of the tooth) root planing and oral hygiene instructions, and 85 were assigned to brushing alone. After 2 months, participants with elevated CRP levels decreased by 38 percent in the treatment group and increased by 4 percent in the comparison group [10]. In another randomized trial of 75 women and men over the age of 40, those with chronic periodontitis had significantly higher levels of CRP than those without elevations. These findings were similar among those with and without CVD.[11] In a recent and novel randomized trial of 61 participants with dental plaque at baseline, a plaque identifying toothpaste produced a highly significant reduction in dental plaque as well as a significant reduction in CRP in a pre-specified subgroup with elevated levels at baseline [12].

Conclusions

The hypothesis that decreasing inflammation reduces risks of cardiovascular disease is strongly supported by the results of two large-scale randomized trials that reduced CRP, one with rosuvastatin, the most potent [13] and the other with canakinumab, a human monoclonal antibody targeted at interleukin-1 beta. It has no cross-reactivity with other members of the interleukin-1 family, including interleukin-1 alpha [14].

In the Justification for the Use of Statins in Primary Prevention Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, 17,802 apparently healthy patients without evidence of a prior coronary event but with CRP levels >2.0, were randomized to either rosuvastatin 20mg daily or placebo.These primary prevention subjects had a moderate risk of a first event because their 10-year risk was about 16-18% and 41% had metabolic syndrome.The selection criterion of risk was an elevation of high sensitivity CRP.The baseline LDL-C levels in these moderate risk primary prevention subjects of about 109 mg/dL (2.82 mmol/L) would not have generally led clinicians to prescribe statins based on the existing US federal guidelines.Following randomization, the achieved LDL-C levels were 55 mg/dL (1.42 mmol/L) in the 20 mg rosuvastatin group and 109 mg/dL (2.82 mmol/L) in the placebo group. The trial was scheduled to terminate after 5 years but after 1.9 years, the independent DSMB unanimously recommended the early termination of JUPITER.Randomized subjects assigned to rosuvastatin 20 mg compared to placebo experienced a statistically extreme (p<0.0001) 44% relative reduction in the primary pre-specified combined endpoint of MI, stroke, unstable angina, revascularization, or CVD death as well as the individual components of MI, stroke and revascularization and a significant 20% RRR in total mortality (p=0.02).These landmark findings support the hypothesis that inflammation plays a major role in the development of clinical events and, further, that decreasing CRP with rosuvastatin decreases risks of CVD. Specifically, JUPITER demonstrated that rosuvastatin significantly lowered CVD events with significant decreases in CRP which were confounded by concomitant significant decreases in lipid abnormalities.

Unlike rosuvastatin, canakinumab has no effect on lipid concentrations. The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial was designed to test the hypothesis of whether reductions in CRP with canakinumab produced clinical benefits on CVD.

CANTOS used computer-generated codes to randomly allocate 10 061 men and women with a history of MI to placebo or one of three doses of canakinumab (50 mg, 150 mg, or 300 mg) given subcutaneously once every 3 months. In a pre-specified secondary analysis designed to address the relationship of CRP reduction to event reduction in CANTOS, the effects of canakinumab were evaluated on rates of major adverse cardiovascular events, cardiovascular mortality, and all-cause mortality according to on-treatment concentrations of CRP. Multivariable modeling was used to adjust for baseline factors associated with achieved CRP and multiple sensitivity analyses performed to address the magnitude of residual confounding. The median follow-up was 3-7 years.

Baseline clinical characteristics did not define patient groups with greater or lesser cardiovascular benefits when treated with canakinumab. However, trial participants allocated to canakinumab who achieved CRP concentrations less than 2 mg/L had a 25% reduction in major adverse cardiovascular events (multivariable-adjusted hazard ratio [HR]=0·75, 95% CI 0·66–0·85, p<0·0001), whereas no significant benefit was observed among those with on-treatment CRP concentrations of 2 mg/L or above (HR=0·90, 0·79–1·02, p=0·11). For those treated with canakinumab who achieved on-treatment CRP concentrations less than 2 mg/L, cardiovascular mortality (HR =0·69, 95% CI 0·56–0·85, p=0·0004) and all-cause mortality (HR=0·69, 0·58–0·81, p<0·0001) were both reduced by 31%, whereas no significant reduction in these endpoints was observed among those treated with canakinumab who achieved CRP concentrations of 2 mg/L or above. Similar differential effects were found in analyses of the prespecified secondary cardiovascular endpoint which additionally included hospitalization for unstable angina requiring unplanned revascularization and in sensitivity analyses alternatively based on median reductions in CRP, on 50% or greater reductions in CRP, on the median percent reduction in CRP, in dose-specific analyses, and in analyses using a causal inference approach to estimate the effect of treatment among individuals who would achieve a targeted CRP concentration. In CANTOS, the magnitude of the CRP

reduction following a single dose of canakinumab might provide a simple clinical method to identify individuals most likely to accrue the largest benefit from continued treatment. These data further suggest that lower is better for inflammation reduction with canakinumab. Thus, CANTOS demonstrated that canakinumab significantly reduced CRP and subsequent CVDwhich were not confounded by concomitant significant decreases in lipid abnormalities.

With respect to interrelations of periodontal disease with CRP, in the pilot trial of the plaque identifying toothpaste, both dental plaque and CRP were significantly decreased.All these findings provide support for the hypothesis that reduction of dental plaque in patients with periodontal disease will decrease inflammation as measured by CRP. As CRP is an accurate measure of inflammation and sensitive marker of CVD it is also plausible to hypothesize that patients with periodontal disease whose CRP is reduced will experience a decrease in risks of CVD. The direct test of this hypothesis requires a large-scale randomized trial of sufficient size and duration designed a priori to do so.Such a finding would have major clinical and public health implications.

Disclosures

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