Published in final edited form as:
Curr Opin Nephrol Hypertens. 2010 November ; 19(6): 519–526. doi:10.1097/MNH.0b013e32833eda38.

Periodontal disease as a risk marker in coronary heart disease and chronic kidney disease

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Abstract

Purpose of review—Over half a million Americans die each year from coronary heart disease (CHD), 26 million suffer from chronic kidney disease (CKD), and a large proportion have periodontal disease (PD), a chronic infection of the tissues surrounding teeth. Chronic inflammation contributes to CHD and CKD occurrence and progression, and PD contributes to the cumulated chronic systemic inflammatory burden. This review examines recent evidence regarding the role of PD in CHD and CKD.

Recent findings—Periodontal pathogens cause both local infection and bacteremia, eliciting local and systemic inflammatory responses. PD is associated with the systemic inflammatory reactant CRP, a major risk factor for both CHD and CKD. Non-surgical PD treatment is shown to improve periodontal health, endothelial function and levels of CRP and other inflammatory markers. Evidence for the association of PD with CKD consists of a small body of literature represented mainly by cross-sectional studies. No definitive randomized-controlled trials exist with either CHD or CKD as primary endpoints.

Summary—Recent evidence links PD with CHD and CKD. Adding oral health self-care and referral for professional periodontal assessment and therapy to the repertoire of medical care recommendations is prudent to improve patients' oral health and possibly reduce CHD and CKD risk.

Keywords

chronic kidney disease; coronary heart disease; inflammation; periodontal disease

Introduction

Coronary heart disease (CHD) and chronic kidney disease (CKD) are important public health concerns. CHD is the leading cause of death [1], and 26 million Americans with CKD

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The authors report no conflicts of interest related to this report.

are more likely to progress to CHD and premature death due to CHD than progress to kidney failure [2]. Multiple studies support the role of PD in contributing to a chronic systemic inflammatory burden in both CHD and CKD. A consensus report simultaneously published in the Journal of Periodontology and American Journal of Cardiology recommended periodontists inform patients with periodontal disease (PD) they may have increased risk for cardiovascular disease and that cardiologists recommend patients have oral health checkups [3**]. Chronic inflammation also contributes to the pathogenesis of hypertension and diabetes, both major risk factors for both CHD and CKD [4]. Health care personnel advise patients to reduce CHD and CKD risk through smoking cessation, diet modification, exercise, and antihypertensive drug therapy, as well as good glycemic control for individuals with diabetes. This review examines the evidence for the role of PD in CHD and CKD to assist health care providers as they consider adding home self-care and referrals for periodontal assessment and therapy to their repertoire of recommendations to improve patient's oral health and thereby possibly reduce risks for CHD and CKD.

Definitions

First, we will define the key terms central for this review.

Periodontal Disease

The term "periodontal diseases" has been used for years to include all diseases of the soft and hard tissue surrounding the teeth (i.e. the periodontium), including gingivitis, which is a reversible infection of the soft tissue without permanent loss of periodontal support. Chronic periodontitis, henceforth referred to as PD, is a chronic bacterial infection that causes a persistent host inflammatory response with destruction of the bone and soft tissue surrounding teeth, leading to tooth mobility and ultimately to loss of teeth. In adults, PD is a major cause of tooth loss, hence edentulism can be regarded as a marker of past PD [5]. Observational and interventional studies use various combinations of clinical and/or radiographic measures of extent and/or severity of gingival bleeding, probing pocket depth, attachment loss, and radiographic bone loss in specifying case definitions for PD [6, 7]. When studying the possible role of PD in systemic conditions, we believe it is the inflammatory component of PD that is important, thus a useful clinical measure of active PD is one that incorporates bleeding on probing as a measure of active inflammation in combination with clinical attachment loss [8, 9**, 10] and/or probing pocket depth [11]. Additional definitions of PD that may be important to studies of the systemic effect of PD are based on serological antibody titers to periodontal pathogens [12*, 13, 14] or clinical measures shown to correlate well with periodontal pathogen antibodies and inflammatory markers [11].

Coronary Heart Disease

CHD, as used in this review, refers to atherosclerosis of the coronary arteries leading to insufficiency of the myocardial blood supply due to reduction of blood flow through one or more of the coronary arteries or its branches [15]. Myocardial infarction, angina pectoris, and ischemic heart disease will be included as CHD in this report [1].

Chronic Kidney Disease

CKD is currently defined by the National Kidney Foundation's Kidney Disease Outcome Quality Initiative's (KDOQI) classification of five stages of increasing severity of CKD based on kidney damage (microalbuminuria) and decreasing kidney function measured as glomerular filtration rate [16].

Risk Marker

A risk marker is an attribute or exposure that is associated with an increased probability of disease but not necessary a causal factor [17]. Thus, a risk marker can be determined based on cross-sectional data. Because most studies of the association between PD and CHD and CKD are of cross-sectional design, we refer to these factors as "*risk markers*".

Conceptual Model Linking PD with CHD and CKD

The conceptual model shown in the Figure is a simplified framework linking PD with CHD and CKD. Chronic inflammation elicits the acute-phase response and other inflammatory mediators that are common risk markers for CHD and CKD [4] and has a fundamental ongoing role in atherosclerosis [18]. As a chronic infection, PD contributes to the cumulative chronic inflammatory burden through the systemic dissemination of inflammatory mediators produced during the local tissue destructive immune-inflammatory response to periodontal pathogens as well as the systemic dissemination of the periodontal pathogens and their products (e.g., lipopolysaccharides) [19].

The link between PD and CKD may be bi-directional, as evidence is emerging to suggest uremia may contribute to increased gingival inflammation in patients on dialysis [20*]. Parenthetically, this bi-directional association is similar to the bi-directional relationship between PD and diabetes [21]. Kidney disease, by virtue of uremia or other mechanisms, may predispose to PD. The systemic inflammatory burden of PD may contribute to endothelial injury and atherogenesis [22*, 23]. The link between CHD and CKD may also be bi-directional. CKD is a well-established risk factor for CHD [2, 4, 16, 24] and clinical atherosclerosis and heart failure have recently been shown to be independently associated with rapid kidney function decline [25*]. It is noteworthy that adults with CKD are more likely to progress to cardiovascular events including CHD and heart failure, than to kidney failure [24].

Empirical Evidence to Support the Conceptual Model

Next, we will briefly describe the scientific evidence supporting each specific component of our conceptual model.

Bacteremia

The periodontal pathogenic bacteria and their byproducts (e.g., lipopolysaccharides) translocate via bacteremia after they easily penetrate the inflamed, ulcerated gingival tissue surrounding the teeth and enter the bloodstream, by which they are dispersed systemically and elicit host responses in distal tissues and organs. Researchers have found periodontal pathogenic bacteria in atherosclerotic plaque [26, 27] and in the arterial walls [28, 29]. Periodontal pathogens are associated with endothelial dysfunction [30].

Periodontopathogen-Specific Immune Response

Elevated *Porphyromonas gingivalis (Pg)* antibody titers have been found to be independently associated with PD, and high *Eubacterium nodatum* titers were associated with periodontal health [12*]. Two other studies also found those with PD had higher *Pg* antibody titer levels, as well as those with CHD [31*, 32]. Periodontopathogen antibody titers are shown to be associated with subclinical atherosclerosis as measured by carotid intima-medial thickness (IMT) [19] and with CHD and CHD death [33], whereas higher *P. intermedia* antibody levels have been found in acute coronary syndrome and coronary artery disease (CAD), suggesting that infection of an atheroma by periodontopathogens may trigger the acute coronary syndrome [10]. Interestingly, antibody titers to *Aggregatibacter*

actinomycetemcomitans, another periodontal pathogen, have been reported to have an independent negative [5] and positive association [34] with CKD. The current evidence from these few reports remains inconclusive but support conducting further investigations to determine the value of measuring antibody titers to periodontal pathogenic bacteria in studying the role of PD in the pathogenesis of CHD and CKD.

Diabetes Duration, Glycemic Control, and Insulin Resistance

Diabetes must be considered in an evaluation of the relationships between PD and CHD and CKD because these three diseases are recognized as complications of diabetes. Further, rigorous management of glycemic control reduces the risk of CHD and CKD in people with diabetes [35], and evidence is emerging that non-surgical periodontal therapy significantly contributes to improvement in glycemic control [35, 36**]. As indicated in the conceptual model (see Figure), there are both direct and indirect effects of diabetes on CHD and/or CKD, with the indirect effects occurring through hypertension [37] and atherosclerosis [38]. In addition, insulin resistance has also been discussed as the metabolic link for PD contributing to poorer glycemic control in diabetes [39].

Hypertension

It is well established that hypertension increases the risk for CHD and CKD occurrence, progression, and mortality [40*, 4], as does lower blood pressure in dialysis patients. Relevant to this review, in cross-sectional studies of moderate-to-severe CKD (Stage 3-4) [5, 9**, 41], and kidney transplantation [42], those with hypertension were twice as likely to have CKD than those without hypertension after simultaneously taking into account other statistically significant risk markers, including PD. A large cross-sectional study provides the first population-based evidence for a direct relationship between the amounts of pathogenic subgingival periodontal bacteria and systolic and diastolic blood pressure, respectively, as well as prevalent hypertension [43**].

Atherosclerosis

Endothelial dysfunction—The inability of arteries and arterioles to dilate (endothelial dysfunction) is a key event in the development of atherosclerosis and precedes clinically obvious vascular pathology by many years. Endothelial dysfunction predicts myocardial dysfunction. Brachial artery flow-mediated dilation is a non-invasive measurement of endothelial dysfunction. A randomized controlled trial (RCT) of intensive periodontal therapy showed significant improvement of flow-mediated dilation [30], suggesting a causal link between PD and endothelial dysfunction as an indicator of early atherosclerosis in otherwise healthy individuals affected by severe PD. In order to elucidate the mechanisms involved, another study investigated the association between PD and circulating endothelial progenitor cells as markers for endothelial dysfunction [44*]. This study showed, for the first time, that moderate-to-severe PD was associated with an increased level of circulating endothelial progenitor cells which were also associated with CRP.

Intima Media Thickness (IMT)—IMT is a measure of subclinical atherosclerosis. A small study of 35 people with mild-to-moderate PD, found non-surgical periodontal therapy reduced levels of inflammatory markers and IMT [22*]. Evidence of a direct relationship between PD and IMT was first demonstrated among 657 dentate subjects when individuals with greater quantities of periodontopathogens had higher mean IMT than individuals with lower quantities. This relationship was independent of CRP, and was specific for pathogenic periodontal bacteria [45].

General Inflammatory Markers

An acute-phase inflammatory response, indicated by elevated CRP levels, is associated with many chronic diseases and is included in the Framingham risk score used to predict coronary death or myocardial infarction [40*]. The U.S. Preventive Services Task Force [46*] concluded from systematic reviews there is strong evidence that CRP is associated with CHD events [47*], but there is insufficient evidence to support reducing CRP levels prevents CHD. An important PD-related RCT is the multicenter Periodontitis And Vascular Events (PAVE) study. This pilot study evaluated the effect of periodontal treatment in preventing a secondary cardiac event in 303 individuals with CHD history by assessing periodontal status and CRP levels [48**]. No change in CRP level was found after treating obese individuals, but significantly fewer non-obese participants had CRP ≥3 mg/l following periodontal treatment. Periodontal therapy did not decrease CRP levels among individuals with CRP levels <3 mg/l at baseline. The authors suggested obesity increased CRP levels and nullified any periodontal treatment effects on CRP reduction.

In addition to CHD, higher CRP levels are independently associated with more rapid loss of kidney function [49]. African Americans are more likely to have CKD than non-Hispanic whites. (Race/ethnicity is another risk marker in the conceptual model depicted in the Figure). Only limited data exist for this racial disparity, which is not fully explained by the higher rates of hypertension, diabetes and obesity. Hence, an important study is the large cross-sectional study of 4,320 African Americans in the Jackson Heart Study that investigated the role of inflammation in CKD and found CRP was independently associated with CKD, but not significantly associated with albuminuria [50*]. This finding adds to the researchers earlier finding that CRP level is heritable after adjusting for age, gender and body mass index [51]. A meta-analysis reported strong evidence for elevated CRP in people with PD compared to those without PD and modest evidence for the effect of non-surgical periodontal therapy decreasing CRP levels [52]. A small RCT showed for the first time that non-surgical periodontal treatment caused a simultaneous reduction in plasma levels of CRP, interleukin(IL)-6, and fibrinogen in subjects with severe periodontitis and severe non-responsive arterial hypertension under medical treatment [53*]. A large population-based study of 4,830 Scottish adults found those who never or rarely brushed their teeth had an increased concentration of both CRP and fibrinogen [54*]. A recent case-control study of 68 cases with severe PD and 48 periodontally healthy controls found PD was associated with increased levels of CRP, glucose, fibrinogen, and IL-18, and with decreased levels of IL-4 [55*]. However, a study of dialysis patients found no association between moderate-to-severe PD and CRP or with serum albumin [56**], even though those with moderate-to-severe PD were five times more likely to die from cardiovascular events than those with no or mild PD. An earlier study by these researchers found severe PD was associated with serum albumin, but not with CRP [57]. An RCT found no significant difference in levels of CRP, IL-6, and plasminogen activator inhibitor-1 between an intensive periodontal treatment group and the community-based periodontal care control groups at 2- and 6-months follow-up examinations [30]. In another study, provision of comprehensive therapy to 30 patients with severe PD resulted in alterations in several inflammatory biomarkers that varied greatly and inconsistently among individuals. These changes were unrelated to severity of the periodontal infection and seemed to depend more on the inflammatory host response. The authors point to atherosclerotic status as a reasonable candidate to investigate as a confounder [58**].

Other Risk Markers

Additional risk markers common to CHD and CKD include smoking, age, race/ethnicity, low income/education, cholesterol, high-density lipoprotein and obesity [16, 40*]. However, the traditional factors explain only about half the deaths from CHD [59], and almost half of

all heart attacks occur in patients without the classic Framingham study risk factors [60]. A candidate-gene association study demonstrated that CHD and PD are genetically related by at least one susceptibility locus, and this shared genetic susceptibility locus did not appear to be modified by the common risk factors for CHD and PD. Hence, the authors conclude the association between these common inflammatory complex diseases could be partially due to a shared genetic cause, thus providing new insight into the underlying partially shared pathogenic mechanisms of these complex common diseases [61**].

Empirical Evidence of the Role of PD in CHD

The effects of PD and treatment of PD are described under the respective headings of the main risk marker measured. A growing body of epidemiologic evidence supports an association between clinically diagnosed PD and CHD [62], and recently, the strength of the evidence for this biologically plausible association was found to be insufficient, but suggestive, of a causal relationship [63**]. Meta-analysis of 22 case-control and cross-sectional studies and 12 cohort studies concluded the risk for ischemic cardiovascular disease was significantly higher among individuals with PD [64**]. A large cross-sectional study of women [65] and a large prospective study of men and women with 12 years follow-up [66*] did not find a statistically significant relationship between probing pocket depth or PD, respectively and CHD, but found a significant association between tooth loss and increased risk for CHD and CHD mortality.

A U.S. cohort study with an average of 2.9 years follow-up of men and women with a history of myocardial infarction showed that loss of periodontal attachment level independently predicts recurrent cardiovascular events among analyses restricted to never-smokers [67**]. Similarly, a longitudinal study of patients with acute coronary syndrome reported PD was strongly associated with both first events and acute coronary syndrome recurrence [68*]. A case-control study of CAD and non-CAD found PD was independently associated with CAD [69].

Empirical Evidence of the Role of PD in CKD

The evidence for the role of PD in CKD prevalence and progression stems mainly from population-based cross-sectional studies, and case-control and smaller clinical studies. The effects of PD have been described under the respective headings of the main risk marker measured. In the context of studies on the relationship between PD and CKD, a population-based cross-sectional study found PD or its severe consequence, edentulism was independently associated with CKD after adjusting for 11 other traditional and nontraditional risk factors [5]. This study is noteworthy because it provided evidence for the importance of simultaneously taking into account other risk factors rather than identifying high-risk subgroups based on a single risk factor. In addition, the dose response for periodontal status was reported such that the odds of CKD increased as the severity or extent of PD increased. This finding is similar to an earlier longitudinal study of 529 Gila River Indian Community adults with type 2 diabetes that found a dose-response between PD (none/mild PD, moderate PD, severe PD, and edentulous) and incidence of macroalbuminuria and end-stage renal disease [70]. Another key finding is a prediction model for CKD in which PD or edentulism was a significant predictor, after controlling for the effect of diabetes (duration), in addition to controlling for high CRP level and eight other commonly recognized risk markers for CKD [9**]. Most importantly, the beta coefficients and formula provided in this report provide the opportunity to estimate anyone’s probability of CKD based on their specific characteristics as expressed by the presence or absence of 12 risk markers.

A highly relevant study of dialysis patients investigated the role of PD in CHD (thus incorporating all three diseases under review) using a well-designed retrospective 18 month follow-up study of 168 dentate adults. The important finding was that patients on dialysis with moderate-to-severe PD were five times more likely to die from cardiovascular disease than those with no or mild PD [56**].

Limitations to Causal Inferences

The major limitation to making unequivocal statements regarding the causal role of PD in the pathogenesis or progression of CHD and CKD is the inability to establish causality due to the cross-sectional study design of most of the large, population-based reports. Other limitations are the small number and lack of consistent findings from well-designed prospective studies, including clinical trials that control for important confounders and effect modifiers, such as smoking, diabetes, hypertension, and obesity.

Conclusion

While the evidence linking PD with CHD and CKD is not yet conclusive, recent evidence strengthens support of the biologically plausible role for PD in the occurrence and progression of CHD and CKD. To better understand the complex relationships between PD, CHD, and CKD, additional well-designed prospective cohort and controlled intervention studies are needed. Nevertheless, adding personal oral hygiene and referral for professional periodontal assessment and therapy to the repertoire of medical care recommendations is prudent to improve patients' oral health and possibly reduce CHD and CKD risk.

Acknowledgments

This work was supported in part by grant NIH DE016031 (MAF).

Supported in part by NIH grant DE016031 to Dr. Monica A. Fisher

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49. Tonelli M, Sacks F, Pfeffer M, et al. Biomarkers of inflammation and progression of chronic kidney disease. Kidney Int. 2005; 68:237–245. [PubMed: 15954913]

50*. Fox ER, Benjamin EJ, Sarpong DF, et al. The relation of C--reactive protein to chronic kidney disease in African Americans: the Jackson Heart Study. BMC Nephrol. 2010; 11:1. http://www.biomedcentral.com/1471-2369/11/1. [PubMed: 20078870] This large cross-sectional study provides much needed data on the racial disparity in which African Americans are more likely to have CKD than non-Hispanic whites. This racial disparity is not fully explained by higher rates of hypertension, diabetes, and obesity, and thus, additional data -- such as this finding that CRP was independently associated with CKD, but not with albuminuria -- raise questions for further studies.

51. Fox ER, Benjamin EJ, Sarpong DF, et al. Epidemiology, Heritability, and Genetic Linkage of C-Reactive Protein in African Americans (from the Jackson Heart Study). Am J Cardiol. 2008; 102:835–841. [PubMed: 18805107]

52. Paraskevas S, Huizinga JD, Loos BG. A systematic review and meta-analyses on C-reactive protein in relation to periodontitis. J Clin Periodontol. 2008; 35:277–290. [PubMed: 18294231]

53*. Vidal F, Figueredo CM, Cordovil I, Fischer RG. Periodontal therapy reduces plasma levels of interleukin-6, C-reactive protein, and fibrinogen in patients with severe periodontitis and refractory arterial hypertension. Journal of Periodontology. 2009; 80:786–791. [PubMed: 19405832] This small study of 11 adults in the treatment group and 11 non-treated controls found non-surgical periodontal treatment improves periodontal status among patients with severe PD and severe refractory hypertension under medical treatment over five years. Periodontal treatment reduced CRP, IL-6, and fibrinogen at the same time.

54*. de Oliveira C, Watt R, Hamer M. Toothbrushing, inflammation, and risk of cardiovascular disease: results from Scottish Health Survey. BMJ. 2010; 340:c2451. http://www.bmj.com/cgi/content/full/340/may27_1/c2451. [PubMed: 20508025] This is the first study to show an association between self-reported toothbrushing and incident cardiovascular disease -- of which 74% was CHD in a large representative sample of adults without overt cardiovascular disease. The causal nature of this association has yet to be determined.

55*. Buhlin K, Hultin M, Norderyd O, et al. Risk factors for atherosclerosis in cases with severe periodontitis. J Clin Periodontol. 2009; 36:541–549. [PubMed: 19538326] This is the first report on the plasma pro-inflammatory cytokine IL-18 levels in PD, although increased levels of IL-18 have been shown to be present in inflamed periodontal tissues and in gingival crevicular tissue destruction.

56**. Kshirsagar AV, Craig RG, Moss KL, et al. Periodontal disease adversely affects the survival of patients with end-stage renal disease. Kidney Int. 2009; 75:746–751. [PubMed: 19165177] This retrospective cohort study is important due to the link found between PD and the very serious outcome, namely that those with moderate-to-severe PD were over 5 times more likely to die from cardiovascular disease than those with no or mild PD.

57. Kshirsagar AV, Craig RG, Beck JD, et al. Severe periodontitis is associated with low serum albumin among patients on maintenance hemodialysis therapy. Clin J Am Soc Nephrol. 2007; 2:239–244. [PubMed: 17699419]

58**. Behle JH, Sedaghatfar MH, Demmer RT, et al. Heterogeneity of systemic inflammatory responses to periodontal therapy. J Clin Periodontol. 2009; 36:287–294. [PubMed: 19426174] The key finding is the large inter-patient variability in pre-and post-intervention concentrations of inflammatory biomarkers, seemingly unrelated to the severity of periodontal infection. Such variance in host response we believe will become a main focus of investigations in the future.

59. National Center for Health Statistics. Deaths and Mortality (Data are for the U.S.): Number of deaths for leading causes of death; Source: Deaths: Final Data for 2006, tables B, D, 7, 30. 2009. http://www.cdc.gov/nchs/fastats/deaths.htm

60. Smith SC Jr. Current and future directions of cardiovascular risk prediction. Am J Cardiol. 2006; 97(2 Supplement 1):28–32.

61**. Schaefer AS, Richter GM, Groessner-Schreiber B, et al. Identification of a shared genetic susceptibility locus for coronary heart disease and periodontitis. PLoS Genetics. 2009; 5:e1000378. [PubMed: 19214202] This report provides new insight into the underlying partially shared risk factors for PD and CHD, such as smoking and diabetes, and involvement of a chronic inflammatory process. Interestingly, the finding of a shared genetic susceptibility locus did not appear to be modified by the common environmental and behavioral risk factors known to increase the susceptibility for CHD and/or PD.

62. Humphrey LL, Fu R, Buckley DI, et al. Periodontal disease and coronary heart disease incidence: a systematic review and meta-analysis. J Gen Intern Med. 2008; 23:2079–2086. [PubMed: 18807098]

63**. Joshipura K, Zevallos JC, Ritchie CS. Strength of evidence relating periodontal disease and atherosclerotic disease. Compend Contin Educ Dent. 2009; 30:430–439. [PubMed: 19757736] This report assessed the evidence supporting causal criteria (specificity, strength of association, dose-response, time sequence, biologic plausibility, consistency, and independence from confounding) relating PD and atherosclerotic disease, including ischemic heart disease.

64**. Blaizot A, Vergnes JN, Nuwwareh S, et al. Periodontal diseases and cardiovascular events: meta-analysis of observational studies. Int Dent J. 2009; 59:197–209. [PubMed: 19774803] Recent and comprehensive meta-analyses of 34 observational studies relating PD to ischemic heart disease due to cardiac atherosclerosis. The paradoxical finding that PD was more strongly

associated with an acute cardiac event (i.e. acute myocardial infarction) than with a chronic cardiac condition (i.e. CHD) needs to be further investigated in future studies.

65. Stenman U, Wennstrom A, Ahlqwist M, et al. Association between periodontal disease and ischemic heart disease among Swedish women; a cross-sectional study. Acta Odontol Scand. 2009; 67:193–199.

66*. Holmlund A, Holm G, Lind L. Number of teeth as a predictor of cardiovascular mortality in a cohort of 7,674 subjects followed for 12 years. J Periodontol. 2010; 81:870–876. 2010. [PubMed: 20350152] A dose-dependent relationship between number of teeth and both all-cause and cardiovascular disease mortality is reported, indicating a possible link between oral health and cardiovascular disease.

67**. Dorn JM, Genco RJ, Grossi SG, et al. Periodontal Disease and Recurrent Cardiovascular Events in Survivors of Myocardial Infarction (MI): The Western New York Acute MI Study. J Periodontol. 2010; 814:502–505. [PubMed: 20367093] When studying smoking-related diseases, it is difficult to fully control for the effect of smoking when investigating the role of other factors. Thus, this longitudinal study is important because the researchers removed the effect of smoking by restricting subgroup analyses to never smokers, and in doing so demonstrated PD was associated with recurrent cardiovascular events. Also, this is one of few studies of a direct, primary outcome as opposed to indirect measures of CHD.

68*. Renvert S, Ohlsson O, Pettersson T, Persson GR. Periodontitis: a future risk for acute coronary syndrome? a follow up study over 3 years. J Periodontol. 2010; 81:992–1000. [PubMed: 20350154] An important Swedish longitudinal study of the role of PD and serum creatinine in both initial and recurrent acute coronary syndrome.

69. Oe Y, Soejima H, Nakayama H, et al. Significant association between score of periodontal disease and coronary artery disease. Heart & Vessels. 2009; 24:103–107. [PubMed: 19337793]

70. Shultis WA, Weil EJ, Looker HC, et al. Effect of periodontitis on overt nephropathy and end-stage renal disease in type 2 diabetes. Diabetes Care. 2007; 30:306–311. [PubMed: 17259499]

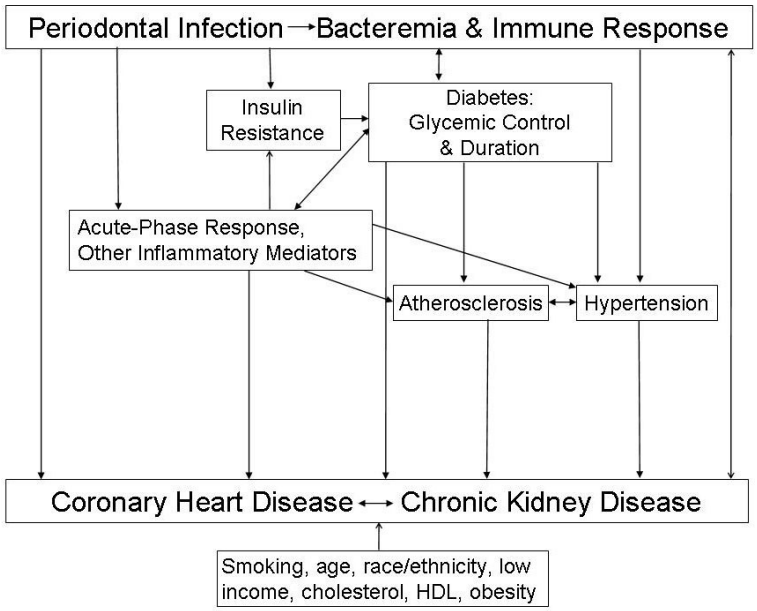

Figure.

Conceptual Model Linking Periodontal Disease with Coronary Heart Disease and Chronic Kidney Disease