

Review

Periodontal Disease in Chronic Kidney Disease and End-Stage Renal Disease Patients: A Review

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Periodontitis · End-stage renal disease · Chronic kidney disease

Abstract

Periodontal disease is a chronic inflammatory disorder and being so it has been associated with accelerated atherosclerosis and malnutrition. Cardiovascular diseases are the leading cause of mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD) patients [National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Annual Data Report, 2010]. A recent scientific statement released by the American Heart Association [Lockhart et al.: *Circulation* 2012;125:2520–2544] claims that, even though evidence exists to believe that periodontal interventions result in a reduction in systemic inflammation and endothelial dysfunction, there is little evidence that those interventions prevent atherosclerotic vascular disease or modify the outcomes. In this review, we discuss the periodontal findings and their association with an increased prevalence of inflammatory markers and cardiovascular mortality in ESRD patients and CKD.

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Introduction

End-stage renal disease (ESRD) patients have a plethora of oral findings. Symptoms include uremic odor, dry mouth, and taste change, and signs can be petechia, ecchymosis and increased tongue coating, and decreased salivary flow [3–5]. Osseous tumors and enlargement have also been described as manifestations of secondary hyperparathyroidism (HPT) [6]. A questionnaire-based survey among hemodialysis (HD) and renal transplant patients by Galili

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et al. [7] demonstrated that these patients showed significantly less dental anxiety than controls and also less concern about oral health.

Periodontal diseases are those involving one or more structures of the periodontium, which includes the alveolar bone, the periodontal ligament, the root cementum, and the gingiva. They are caused by pathogenic microflora in the biofilm or dental plaque that forms adjacent to the teeth on a daily basis. Inflammation that is confined to the gingival tissue is known as gingivitis, and inflammation that extends deep into the tissues and causes loss of supporting connective tissue and alveolar bone is known as periodontitis [8]. Plaque-induced inflammatory lesions make up the vast majority of periodontal diseases and have traditionally been divided into two categories: gingivitis or periodontitis. While in some sites or individuals, gingivitis never progresses to periodontitis, data indicate that gingivitis always precedes periodontitis.

Pathogenesis of Periodontitis

Decreased Salivary Production

Salivary scintigraphic studies on patients with ESRD have shown decreased salivary flow compared to the normal population [4]. Apart from a decreased secretion of saliva, ESRD patients are usually restricted in fluid intake for concerns of volume overload [9]. Xerostomia may predispose to caries, mucositis, and oral infection as the protective factors in saliva are diminished. Further, dialysis duration and end-stage renal failure significantly correlate with gingivitis, probing depth, attachment loss, and enamel hypoplasia.

Salivary Chemistry

ESRD patients, when compared to the general population, have increased salivary pH and salivary urea concentrations [10]. Martins et al. [11] studied salivary parameters in 15 ESRD patients on HD before and after dialysis treatment and compared them with age-matched controls. This study found that there were statistically significant differences in the levels of protein, potassium, magnesium, and phosphorus concentrations. In a study which compared salivary findings between diabetic and nondiabetic patients, Chuang et al. [12] found that diabetic patients had a higher caries rate and lower salivary pH. These patients also have higher salivary phosphate levels and are hence predisposed to calculus formation [13].

Microbiology of Periodontal Infection

Among the normal commensal in the subgingival area, Gram-positive organisms predominate in the periodontally healthy population [14]. However, in the periodontally diseased population, there is an increased prevalence of Gram-negative organisms [15]. These Gram-negative organisms produce endotoxins which are capable of invoking inflammatory and immune responses. Progressive periodontal disease may increase the antigenic exposure of the host to bacterial antigens, as evidenced by increasing antibody titers to *Porphyromonas gingivalis* in one study [16].

Hyperparathyroidism

Secondary HPT is a frequent complication in ESRD patients. Even though animal studies have shown that elevated parathyroid hormone levels have been associated with higher levels of proinflammatory cytokines in the gingival tissue [17], in one study of 35 ESRD patients, secondary HPT did not have an appreciable effect on periodontal indices and radiographic bone height [10]. Hence, the role of secondary HPT in periodontal diseases remains unclear.

Studies in ESRD and Chronic Kidney Disease Patients with Periodontitis (table 1)

Gavalda et al. [18] studied dental, periodontal, oral mucosal, and salivary findings in 103 adult ESRD patients on HD and compared them with those of 53 age- and sex-matched healthy controls. The results showed significantly higher plaque and calculus indices and lower salivary secretion among the HD patients compared with healthy controls.

Cengiz et al. [19] evaluated the periodontal status in continuous ambulatory peritoneal dialysis (CAPD) patients and found poor periodontal health in 85.5% of the patients. Multiple regression analysis revealed that age, albumin level, and duration of dialysis were independently associated with the severity of periodontitis in CAPD patients. A higher percentage of patients in the severe periodontitis group had malnutrition, inflammation, and atherosclerosis [19].

Joseph et al. [20] studied 77 patients with chronic kidney disease (CKD) for oral hygiene status, gingival inflammation, probing pocket depth, and clinical attachment loss. The subjects were grouped into three categories (no/mild, moderate, and severe periodontitis). All periodontal parameters were significantly elevated in the case group as compared to controls [20].

In one study by Rahmati et al. [21], sera from 86 consecutive dentate HD patients were assayed for levels of immunoglobulin G antibody to six periodontal species by means of an enzyme-linked immunosorbent assay. log serum immunoglobulin G antibody levels to *P. gingivalis* also were significantly greater in the group with elevated C-reactive protein (CRP) levels. Univariate comparisons between the subjects with or without elevated CRP levels (>10 mg/l) showed that CRP level elevation was associated significantly ($p < 0.05$) with greater doses of recombinant human erythropoietin and lower levels of hemoglobin, serum iron, transferrin saturation, albumin averaged over the 3 preceding months, total cholesterol, and triglycerides.

Inflammatory Markers and Periodontitis in ESRD Patients

Inflammatory and prothrombotic markers are predictors for a worsening of kidney function [22]. ESRD patients are at risk for having a proinflammatory state due to a variety of reasons, particularly infection involving dialysis access catheters, exposure to dialysis membranes, and volume overload.

In an effort to investigate the possible adverse effects of periodontitis in 255 maintenance HD patients, Chen et al. [23] compared periodontal severity with malnutrition and inflammation. Plaque index, gingival index, periodontal disease index, albumin, blood urea nitrogen, creatinine, transferrin, absolute lymphocyte count, normalized protein catabolic rate, high-sensitivity CRP, and ferritin were analyzed. The results showed that 80% of HD patients had poor oral health. Aging, smoking, diabetes, and longer dialysis duration were independently associated with the severity of periodontitis. Patients with more severe periodontitis had higher percentiles of malnutrition and inflammation.

Kadiroglu et al. [24] studied hematologic indices, CRP levels, and periodontal disease indices (plaque index, gingival index, probing pocket depth, and periodontal disease index) before and after periodontal therapy in 41 HD patients on recombinant human erythropoietin therapy. They found that the mean CRP level and erythrocyte sedimentation rate decreased and that the hemoglobin level increased, suggesting a decrease in inflammatory state.

Kshirsagar et al. [25] studied levels of serum albumin and CRP among patients on HD. In this study, patients with severe periodontitis had low serum albumin levels (odds ratio 8.20; 95% confidence interval 1.61–41.82; $p = 0.01$) compared with individuals without severe

Table 1. Studies in ESRD and CKD patients with periodontitis

Study	Patients n	Age years	Design	Objective	Outcome
Gavalda et al. [18]	103	58.9±14.9	Case-control study	Dental periodontal, oral mucosal, and salivary condition in HD patients compared to healthy controls	Significantly higher plaque and calculus indices and lower salivary secretion in HD patients
Cengiz et al. [19]	110	44.3±0.6	Cross-sectional observational study	Compare periodontal disease severity with inflammation and malnutrition in CAPD patients	Periodontal health is poor in CAPD patients and correlates with markers of malnutrition, inflammation, and atherosclerosis
Chen et al. [23]	253	58.8±0.8	Cross-sectional observational study	Explore relationship between periodontal disease, malnutrition, and inflammation by performing clinical examinations on HD patients	Significant association between severe periodontitis and decreased levels of negative acute-phase reactants
Kadiroglu et al. [24]	41	43.1±13.1	Case-control study with intervention	Evaluate association between CRP levels and the periodontal status of HD patients	Periodontal disease is an important source of chronic inflammation in HD patients and can cause hyporesponsiveness to recombinant human erythropoietin treatment
Kshirsagar et al. [25]	154	54.6	Cross-sectional observational study	Study relationship between PD and two measures of systemic inflammation (serum albumin and CRP)	Severe periodontitis was associated with low serum albumin, and no association between severe periodontitis and CRP was found
Rahmati et al. [21]	86	53.3±16.1	Case-control study	Evaluate if destructive periodontal disease could contribute to elevated CRP values in HD populations	HD patients with destructive periodontal disease had elevated CRP values
Grubbs et al. [26]	6,199	21–75	Cross-sectional analysis of NHANES data	Study association between CKD and periodontal disease across various subpopulations	Association between periodontal disease and CKD is not significantly different among subgroups
Beck et al. [27]	1,147		Cohort study	Role of chronic Gram-negative infections in periodontal disease and atherosclerosis	Levels of periodontal disease and incidence of total CHD and fatal CHD indicated a biologic gradient between the severity of exposure and the occurrence of disease
Kshirsagar et al. [38]	168	52/55	Prospective cohort study	Examine the relationship between periodontitis severity and cardiovascular disease mortality	Mild or no periodontal disease compared to moderate-to-severe periodontal disease was significantly associated with death from cardiovascular causes
Bahekar et al. [39]	86,092	20–84	Meta-analysis of case-control studies	Determine relationship between periodontal disease and CHD	Statistically significant positive correlation between periodontal disease and CHD
Fisher et al. [41]	11,211	>18	Population-based cross-sectional study	Possible bidirectional relationship between CKD and periodontal disease, diabetes and hypertension	Bidirectional relationship between periodontal disease and CKD as well as mediation of the effect via diabetes duration and hypertension

Table 1 (continued)

Study	Patients n	Age years	Design	Objective	Outcome
Elter et al. [46]	22	42	Single-masked pilot clinical trial	Determine if periodontal therapy would improve endothelial function and serum inflammatory markers	Improvement in endothelial function may be possible through elimination of chronic oral infection
D’Aiuto et al. [45]	65	48	3-arm preliminary randomized trial	Test effects of standard and intense periodontal therapy on the systemic inflammatory status of healthy individuals suffering from severe, generalized periodontitis	Standard and intense periodontal therapy resulted in significant reductions in CRP levels compared with untreated controls
Mattila et al. [47]	30	50	Interventional case-control study	Investigate whether treatment of periodontitis can decrease the levels of inflammatory markers	Periodontal treatment decreases CRP levels in patients and may thus decrease their risk of CHD
Paraskevas et al. [43]	448		Meta-analysis of 10 cross-sectional studies and 4 interventional studies	Examine the robustness of observations that CRP in periodontitis and the effect of periodontal therapy on CRP levels	Periodontal treatment seemed to significantly lower CRP levels

periodontitis disease after adjustment for several factors. There was no association of CRP levels and severity of the disease.

Grubbs et al. [26] analyzed NHANES data on 6,199 adult dentate participants (aged 21–75 years) with periodontal exams. The estimated prevalences of moderate/severe periodontal disease and CKD were 5.3 and 10.6%, respectively. Periodontal disease was associated with a more than two-fold higher risk of CKD that was moderately attenuated after adjustment for other traditional risk factors and quality dental care. There were no statistically significant interactions between periodontal disease and race/ethnicity, educational attainment, or poverty status. Less-than-recommended dental care was associated with periodontal disease and CKD and was increasingly prevalent among nonwhites and participants with lower educational attainment and lower poverty status [26].

Beck et al. [27] studied a cohort of 1,147 men during 1968–1971 for mean periodontal bone loss scores and worst probing pocket depth scores per tooth. During the follow-up, 207 men developed coronary heart disease (CHD), 59 died of CHD, and 40 had strokes. Incidence odds ratios adjusted for established cardiovascular risk factors were 1.5, 1.9, and 2.8 for periodontal bone loss and total CHD, fatal CHD, and stroke, respectively. Levels of bone loss and cumulative incidence of total CHD and fatal CHD indicated a biologic gradient between the severity of exposure and the occurrence of disease [27]. The hypothesis is that periodontal disease provides an endotoxin burden and inflammatory cytokines (especially TxA₂, IL-1 β , PGE₂, and TNF- α) which serve to initiate and exacerbate atherogenesis and thromboembolic events.

There are a multitude of epidemiological studies which confirm an association between periodontal disease and cardiovascular disease [28–37]. Similar results have been found in ESRD patients with periodontitis. Kshirsagar et al. [38] examined the relationship between periodontitis and cardiovascular disease in 168 HD patients. In this retrospective analysis, compared to the ones with mild or no periodontal disease, patients with moderate-to-severe

disease were at a significantly greater risk for death from cardiovascular causes. In a meta-analysis of 5 prospective cohort studies, Bahekar et al. [39]. found that individuals with periodontal disease had a higher risk of developing CHD than controls. The authors also found that CHD was significantly more severe among individuals with periodontal disease than in those without periodontal disease. However, in one study involving two dialysis centers in Germany, Ziebolz et al. [40] found that 83% of HD patients had minor localized or generalized signs of gingival inflammation, high proportion of missing teeth, and a good level of restoration of caries. The authors conclude that these findings were comparable to the general population in Germany. However, the study is limited by the small study population and the noninvasive nature of dental examination. In addition, oral hygiene in German HD patients may be better than in other countries [40].

Discussion

From the evidence presented above, it is clear that the presence of periodontitis and chronic inflammation in renal patients is associated with an increased risk of cardiovascular death. However, cause-effect relationships between periodontitis, renal disease, chronic inflammation, and cardiovascular death are not established. In this setting, we have a few unanswered questions: (1) Does periodontal disease predispose to systemic chronic inflammatory syndromes in cardiovascular disease and CKD? (2) Does systemic chronic inflammation predispose to periodontal disease? (3) Are both of the above true? (4) If so, does this represent a vicious cycle?

Fisher et al. [41] used a two-step analytic approach and multiple logistic regression models of data from 11,211 adults aged >18 years (NHANES III). They used tests for mediation and structural equation models to examine more complex direct and indirect effects of periodontal disease on CKD, and vice versa. In these two separate models, periodontal disease (adjusted odds ratio 1.62), edentulism (adjusted odds ratio 1.83), and the periodontal disease score were associated with CKD when simultaneously adjusting for 14 other factors. The end results demonstrated a bidirectional relationship between periodontal disease and CKD – meaning each being a risk factor for the other [41]. Interestingly, diabetes and periodontal disease appear to share a bidirectional relationship [42].

Few studies have evaluated the effect of treatment of periodontal disease on inflammatory markers and endothelial dysfunction [43–48]. However, we are in need of larger studies to assess the benefits of periodontitis treatment in CKD/ESRD patients. An exploratory randomized trial by Wehmeyer et al. [49] demonstrated that cooperation between dentists and nephrologists can result in successful recruitment, treatment, and retention of dialysis patients with periodontitis.

Regardless of the poorly understood relationships between periodontitis, renal disease, chronic inflammation, and cardiovascular death, it is reasonable to increase our efforts to prevent, diagnose, and treat periodontal disease. Treating periodontal disease may decrease the proinflammatory state in this population. It may also decrease the oral discomfort and improve nutritional status. Patient with periodontal disease may prefer liquids over solids owing to discomfort and this may also contribute to decreased nutritional status and volume overload. Both could potentially be improved by improving the periodontal health. Periodontitis is common but largely preventable and is usually the result of poor oral hygiene.

Daily brushing and flossing and regular professional dental cleanings can greatly reduce the chance of developing periodontitis. The treatment of periodontal disease begins with the removal of subgingival calculus (tartar) by the nonsurgical procedure known as scaling and root planing. Dental calculus, commonly known as tartar, represents mineralized bacterial

plaque and is comprised almost entirely of calcium phosphate. Clinically, calculus tenaciously adheres to teeth and requires mechanical scraping for removal. Extensive surgical treatment includes flap surgery (pocket reduction surgery), soft tissue grafts, bone grafting, and guided tissue regeneration. The supplemental use of local antibiotics as well as local antiseptic drugs and the systemic use of antibiotics have been shown to provide some benefit compared with debridement alone. However, this benefit is clinically small compared with the effects of local mechanical therapy alone [50].

Conclusion

Regardless of the poorly understood relationships between periodontitis, renal disease, chronic inflammation, and cardiovascular death, it is reasonable to increase our efforts to prevent, diagnose, and treat periodontal disease in CKD and ESRD patients.

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