# Periodontal disease adversely affects the survival of patients with end-stage renal disease

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Periodontal disease is associated with cardiovascular disease and is thought to accelerate systemic atherosclerosis. Here we examined the relationship between periodontitis and cardiovascular disease mortality in outpatients on hemodialysis using a retrospective analysis of 168 adult patients in New York City and North Carolina. During 18 months of follow-up, cardiovascular disease and all-cause mortality were determined from a centralized dialysis registry. One hundred patients had mild or no periodontal disease but the remaining 68 had moderate-to-severe disease defined as 2 or more teeth with at least 6 mm of inter-proximal attachment loss. At baseline, the proportion of males was significantly lower in the moderate-to-severe group. Compared with mild or no periodontal disease, moderate-to-severe disease was significantly associated with death from cardiovascular causes. Adjustment for age, gender, center and dialysis vintage, smoking status, and history of diabetes mellitus or hypertension did not diminish the strength of this association. Our findings suggest a need for larger studies to confirm this connection, along with intervention trials to determine if treating periodontitis reduces cardiovascular disease mortality in dialysis patients.

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Atherosclerosis is thought to be an inflammatory disease.[1] Chronic periodontitis, caused by subgingival infection with predominantly gram negative anaerobic bacteria in disease susceptible individuals, can contribute to systemic inflammation (Figure 1).[2–4] Periodontal pathogens are capable of invading the systemic circulation and of stimulating an hepatic acute phase response.[5,6] In addition, some periodontal pathogens are capable of invading the endothelium of major elastic arteries[7] and atheromatous plaques.[8,9]

Most epidemiological studies have found periodontitis to be associated with cardiovascular disease (CVD), even after adjustment for a variety of medical and socioeconomic confounders.[2–4] Intervention studies have shown that the treatment of periodontal disease improves serum inflammatory markers[10,11] and flow-mediated arterial dilation,[12–16] a marker of endothelial function that becomes dysfunctional early in the course of atherosclerosis.

Recent evidence suggests a high prevalence of periodontitis in individuals with early stages of chronic kidney disease (CKD)[17–19] as well as in those with end-stage kidney disease.[20,21] We postulated that the presence of periodontal disease may adversely affect CVD mortality in a population with a high burden of CVD, namely patients with CKD. We examined the relationship between periodontitis and CVD mortality in a cohort of patients receiving chronic outpatient hemodialysis.

## RESULTS

At the 4 dialysis units, a total of 523 patients were potentially eligible for the study and were evaluated for participation by two study examiners (AK and MY), Figure 2. Several patients refused participation ($n = 199$), whereas others could not participate because of a lack of teeth ($n = 156$). A total of 168 subjects had dental examinations for the evaluation of periodontal disease; 106 at the units in New York City and 62 at the units in North Carolina. A total of 100 subjects had
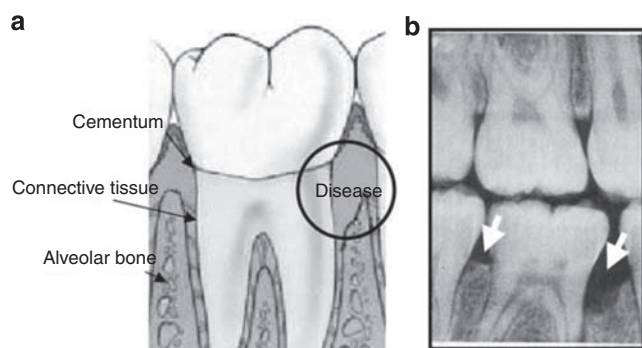
**Figure 1 | Periodontal disease and destruction.** Periodontal tissues and disease destruction. (**a**) Diagram depicts a tooth with the periodontal tissues (cementum, connective tissue, and alveolar bone) being healthy on the left side and compromised due to periodontal disease on the right side of the tooth. Tissues are labeled and arrows point to the corresponding areas. (**b**) Radiograph of molar teeth. Local destruction of supporting alveolar bone due to periodontal disease is demonstrated by the right arrow, while bone levels are shown to be optimal by the left arrow. (From Reference 4, all permissions granted from the New York Academy of Sciences)
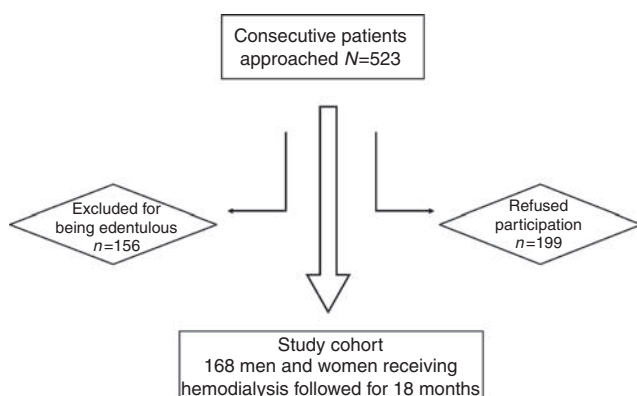


**Figure 2 | Flow diagram of patient enrollment into cohort.**

mild or no periodontal disease, and 68 had moderate-to-severe disease (Table 1).

At baseline, the two groups differed only with respect to the proportion of females. Notably, there was no difference in measured baseline CVD risk factors, including prevalent hypertension, prevalent diabetes mellitus, smoking status, and blood pressure. There were also no differences in the cause of end-stage renal disease (ESRD), type of dialysis access, dialysis adequacy, dialysis vintage, and measures of renal osteodystrophy between the two groups. Finally, average values of serum albumin were comparable between the two groups; both groups had elevated levels of CRP that were not significantly different.

During the 18-month follow-up period, there were 22 deaths; 14 of the deaths were from CVD, while 8 were from other causes (Table 2). Survival by periodontal status is displayed in Figure 3 as a Kaplan–Meier survival plot. Moderate-to-severe periodontitis was significantly associated with CVD mortality compared with mild or none periodontitis, hazards ratio (95% confidence interval) 5.3 (1.5–18.9), $P = 0.01$; Table 3. Subsequent adjustment for a variety of co-variables, including age, sex, center, dialysis vintage, smoking, diabetes mellitus, and hypertension, did not significantly alter the strength of association, HR 5.0 (95% confidence interval, 1.2-19.1; $P = 0.02$).

Moderate-to-severe periodontitis was not significantly associated with all cause mortality, hazards ratio (95% confidence interval) 1.8 (0.7–4.5) compared with mild or none periodontitis.

## DISCUSSION

In this retrospective cohort study, we observed that moderate-to-severe periodontal disease was strongly associated with CVD mortality. Patients with severe-to-moderate periodontal disease had a 5-fold increase in CVD death after 18 months of follow-up. Adjustment for available demographic and medical characteristics did not eliminate the association. We did not observe an association of moderate-to-severe periodontal disease with all-cause mortality, possibly suggesting a degree of specificity to CVD morbidity.

Complications from coronary heart disease and cerebrovascular disease remain the leading causes of mortality and morbidity in the ESRD population.[22] Conventional, Framingham-type risk factors for atherosclerosis may only account for 50 to 70% of atherosclerotic events.[23] Nonconventional risk factors for accelerated atherosclerosis in CKD include anemia, high pulse pressure, disordered mineral and vitamin D metabolism, and hyperhomocystinemia, and possibly, increased oxidative stress.[24,25] Inflammation is closely linked to increased oxidative stress.

Biofilms in the oral cavity contain greater than $10^{10}$ organisms[3] many of which are pathogenetic for periodontitis. Monocytes and dendritic cells within local periodontal tissues recognize bacterial cell wall lipopolysaccharides and other toll-like receptor-agonists. These cells secrete various inflammatory mediators, including prostaglandin E$_2$, interleukin-1β, interleukin-6, and tumor necrosis factor-α.[2,5] Gingival pathogens, also capable of invading the systemic circulation, can affect the host through one of two inter-related mechanisms. First, these organisms promote hepatic activation and release of acute phase reactants, such as interleukin-6 and CRP.[5,6] High circulating levels of CRP may then activate complement.[26] Furthermore, CRP has also been demonstrated to cause calcium dependent binding and aggregation of LDL and very LDL cholesterol.[27]

Second, the organisms, especially *P. gingivalis*, can invade the human endothelial cells (see Despande *et al.*,[7] Dorn *et al.*[8]) endothelial lining and atheromatous plaques.[9] It is highly likely that these organisms can alter endothelial function, platelet function, and plaque stability. A recent study demonstrated that infection of human aortic endothelial cells with *P. gingivalis* promoted adhesion of monocytes

**Table 1 | Baseline demographic and medical characteristics by periodontal disease status (mean and standard deviation for continuous variables and frequency for categorical variables)**

| Variable | None/mild periodontitis N=100 | Moderate/severe periodontitis N=68 | P value |
|---|---|---|---|
| Age, years | 52.2 (13.0) | 55.7 (13.3) | 0.23 |
| Sex male | 54% | 34% | 0.01 |
| Race (non-Hispanic white) | 15% | 9% | 0.23 |
| *Cause of ESRD* | | | 0.63 |
|    Hypertension | 57% | 50% | |
|    Diabetes mellitus | 19% | 27% | |
|    Glomerulonephritis | 8% | 7% | |
|    Polycystic kidney disease | 1% | 3% | |
|    Other[a] | 15% | 13% | |
| Dialysis vintage, years | 3.8 (2.7) | 4.0 (3.8) | 0.67 |
| Hypertension | 84% | 91% | 0.18 |
| Body mass index | 28.3 (6.7) | 28.9 (8.6) | 0.62 |
| Current smoker | 79% | 66% | 0.07 |
| High school education or lower[b] | 61% | 59% | 0.74 |
| Systolic blood pressure, mm Hg | 153 (2.2) | 152 (2.9) | 0.80 |
| Diastolic blood pressure, mm Hg | 82 (1.3) | 83 (1.6) | 0.75 |
| *Vascular access* | | | 0.31 |
|    Fistula | 24% | 65% | |
|    Graft | 23% | 18% | |
|    Catheter | 53% | 17% | |
| Serum albumin, mg/100 ml | 3.9 (0.4) | 3.9 (0.4) | 0.61 |
| C-reactive protein, mg/l | 8.5 (17.8) | 6.5 (11.2) | 0.23 |
| Serum calcium, mg/100 ml | 9.2 (0.9) | 9.3 (0.7) | 0.52 |
| Serum phosphorus, mg/100 ml | 5.8 (1.7) | 5.8 (1.6) | 0.76 |
| Serum PTH, pg/ml | 363 (355) | 450 (344) | 0.21 |
| Serum total cholesterol, mg/100 ml | 148 (35) | 144 (35) | 0.57 |
| Dialysis adequacy (ekDrT/V) | 1.39 (0.04) | 1.44 (0.04) | 0.32 |
| Serum ferritin, mg/l | 432 (345) | 410 (278) | 0.15 |

ESRD, end-stage renal disease.
[a]Other includes unknown, failed kidney transplant, obstruction, congenital abnormalities, acute kidney injury without recovery.
[b]Available only for patients from New York City dialysis clinics.

**Table 2 | Causes of death for study subjects**

| Cause of death | | | |
|---|---|---|---|
| **Cardiovascular disease** | | **Other** | |
| Cardiac arrest | 10 | Sepsis | 2 |
| Cerebrovascular accident (hemorrhagic) | 2 | Respiratory failure | 1 |
| Cardiomyopathy | 1 | Cachexia | 1 |
| Pericarditis | 1 | Accident | 1 |
| | | Hemolytic uremia syndrome | 1 |
| | | Tuberculosis | 1 |
| | | Unknown | 1 |
| **Totals** | **14** | | **8** |



**Figure 3 | Kaplan–Meier survival curve ($P = 0.01$).**
Perio, periodontal disease.

and T-cells.[28] Another related study showed that infection of human aortic endothelial cells promoted coagulation by raising levels of tissue factor and lowering levels of tissue plasminogen activator.[29] Finally, a study of subjects with severe periodontitis showed increased platelet activation compared with healthy controls.[30] Speculatively, the net effect of systemic invasion by these organisms would be to adversely affect endothelial function,[31–33] and thrombosis, important precursors of clinical CVD.

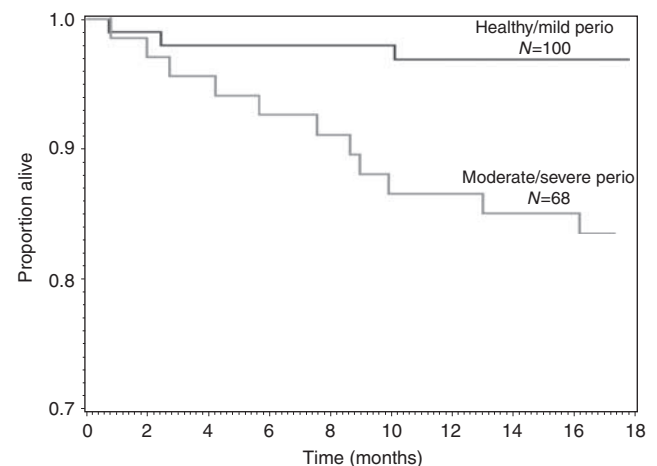Epidemiological studies have confirmed an association between periodontitis and CVD.[2–4] A recent meta-analysis of all available type of association studies—prospective cohort studies, case–control studies, and cross-sectional studies, consistently demonstrated a direct association of periodontal disease and coronary heart disease.[34] Intervention studies have demonstrated a reduction in the systemic levels of CRP, interleukin-6, and LDL-cholesterol following periodontal therapy.[10,11] Several independent intervention trials have

**Table 3 | Hazard ratio (95% confidence interval) for death from CVD by periodontal disease status model with the none/mild group as the referent**

|  | None/mild periodontitis | Moderate/severe periodontitis | P value |
|---|---|---|---|
| Model 1 | 1.00 | 5.3 (1.5–18.9) | 0.01 |
| Model 2 | 1.00 | 5.7 (1.5–21.2) | 0.009 |
| Model 3 | 1.00 | 5.0 (1.2–19.1) | 0.02 |

Model 1: Univariate.
Model 2: Model 1 and age, center, sex.
Model 3: Model 2 and dialysis vintage, smoking status, cause of end-stage renal disease (ESRD) diabetes mellitus, cause of ESRD hypertension.

demonstrated improved flow-mediated dilation following periodontal therapy for up to 6 months after therapy.[12–16]

Our study has important limitations, most reflecting the nature of a retrospective cohort analysis. First, and foremost, we did not have baseline measurements of the burden of CVD. Thus, the observed findings may have been confounded by the presence of variable degrees of occult CVD. Alternatively stated, if periodontitis is predictive of future CVD events, it follows that it would also be associated with baseline CVD. It is important to note that in our study risk factors for baseline CVD, total cholesterol, age, smoking, diabetes mellitus, and hypertension did not vary significantly between the two groups. Yet, we cannot exclude the possibility of residual confounding from variables that were not explicitly measured or from those that were differentially associated with the currently measured variables.

Second, we did not have complete information on socioeconomic status or nutrition. It has been proposed that the observed association between periodontal disease and CVD is confounded by SES, diet, and access to dental care. Yet, the general dialysis population in the United States is generally homogenous with respect to income, disability, and insurance status.

Third, our sample size was modest. Thus, even though the magnitude of the hazards ratio is large with regard to potential clinical impact, the confidence intervals are wide. Furthermore, the small number of incident events limits the potential adjustment variables, and in fact, over-adjustment remains a distinct possibility in our models.

Fourth, we could not confirm the cause of death for patients. The majority of deaths were reported to be from cardiac arrest. Although it seems reasonable to assume that the sentinel event prior to cardiac arrest was an ischemic coronary event and/or arrhythmia, it remains an assumption.

Finally, the small number of deaths, both all-cause and cardiovascular, suggest that the observed population may have been healthier than the average patient receiving hemodialysis. Over 50% of available patients were not included in the study for either edentulousness or refusal to participate. It is unclear whether this affected the validity of the observed association, but it may affect generalizability to the overall ESRD population. In future studies, it will be important to examine baseline characteristics of edentuluous patients or those declining participation.

Paradoxically, the two groups of patients did not vary with respect to the average values of CRP and serum albumin at baseline. For CRP, others have demonstrated a similar lack of association of CRP with periodontal disease in the ESRD population.[20,21] In a group of patients with Stages 3 and 4 CKD, furthermore, we also observed that there was no association of periodontal disease and CRP.[18] A potential explanation for serum albumin is less forthcoming. It may relate to the severity of periodontal disease captured by the current definition of periodontitis; that is, serum albumin does not decrease until there is greater severity of periodontal disease. Alternatively, the lack of association suggests investigation of other potential mechanisms to explain the observed periodontitis and CVD mortality relationship, such as direct invasion of the vasculature and/or destabilization of the endothelium and atheromas by periodontal organisms. At the very least, the findings of this preliminary study need replication.

In this preliminary study, moderate-to-severe periodontal disease was strongly associated with CVD mortality in a cohort of dialysis patients. Given the high burden of unexplained CVD among ESRD patients and among the larger CKD population (in excess of 18 million), investigation of mutable new risk factors appears to be a logical next step. Future studies should examine whether the treatment of periodontitis could improve CVD morbidity and mortality among individuals at various stages of CKD, including those receiving hemodialysis.

## MATERIALS AND METHODS

Between January 2001 and December 2005, patients were enrolled in a study to determine the prevalence of periodontal disease in the end-stage kidney disease population. The study was based at two separate sites in a total of 4 dialysis units, 2 in central North Carolina and 2 in New York City. To be eligible for the study, patients had to be older than 18 years, have a dialysis vintage of at least 3 months, be English speaking, and have at least one natural tooth. Two study authors (AVK and MY) approached patients consecutively and obtained informed consent. Six dental examiners, all trained and calibrated at the University of North Carolina at Chapel Hill (under the guidance of study author JDB), performed the periodontal evaluation. Four of the dental examiners performed the periodontal evaluation in North Carolina, whereas 2 did so in the New York City. The protocol was approved by the Committees on Research Involving Human Subjects at UNC School of Medicine and the New York University School of Medicine Institutional Board of Research Associates.

During the hemodialysis session, trained and calibrated examiners evaluated six sites per tooth (up to 32 teeth per patient). Standard measures of periodontal health were recorded including gingival recession (the linear distance in millimeters between the gingival margin and the cementoenamel junction), and probing depth (the linear distance in millimeters from the gingival margin to the base of the periodontal pocket). Attachment level, a measure of destructive periodontitis, was calculated as probing depth minus the cementoenamel junction measurement.

Periodontal disease was defined by the presence of significant attachment (level) loss and pocket depth. Moderate-to-severe periodontitis was defined as 2 or more teeth with at least 6 mm interproximal attachment level and at least 1 site with probing depth >5 mm. Mild or no periodontitis was defined by the absence of these findings.

Demographic and medical information was abstracted from patient charts as well as by direct interview by two of the study authors (AVK and MY). Neither interviewer/data abstractor was aware of the periodontal disease status of the participants at the time of data abstraction. Age was determined in years at the date of the examination. Gender, race, and smoking status (current, former, never) were determined by self-report at the time of dental evaluation. Information on duration of dialysis and cause of end-stage kidney disease was obtained from the Medicare 2720 form. Laboratory information was obtained from a central laboratory, SPECTRA, for serum measurements: albumin, calcium, phosphorus, parathyroid hormone, cholesterol, ferritin, and dialysis adequacy (equilibrated Kt/V). Information on dialysis access (graft, fistula, or catheter) was obtained from a computerized central registry of patient information at Renal Research Institute. Serum C-reactive protein was determined by a high sensitivity assay of blood drawn from participants on the day of the evaluation. It was not available in the SPECTRA laboratory system.

Information on death was obtained from a centralized computer database of patients at dialysis centers managed by Renal Research Institute. The cause of death was determined by physicians rounding at the different dialysis centers, and then entered into a centralized, computerized dialysis registry by the nurse manager at each unit. The unique study identification number was used to link the participating patient with the registry data.

## Statistical analysis

We first compared patient characteristics by periodontal disease using *t*-tests for continuous variables and Chi-squared tests for categorical variables. CVD death was defined as death ascribed to coronary heart disease (cardiac arrest), pericardial disease, cardiomyopathy, and cerebrovascular disease (including thrombotic and hemorrhagic cerebrovascular events).

Observed survival time was assessed starting from the time of subject enrollment (clinical periodontal examination). Follow-up time was ascertained on all patients up to 18 months after determination of periodontal disease status. Kaplan–Meier survival analysis was used to determine CVD mortality, cardiac mortality, and all-cause mortality at 18 months. Cox proportional hazards ratios were used to determine the risk of death over time after adjusting for important demographic and medical characteristics. The threshold for statistical significance was set at a *P* value of less than 0.05. All analyses were performed using SAS, version 9.2.

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