Association between periodontitis and mortality in stages 3–5 chronic kidney disease: NHANES III and linked mortality study

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Abstract

Introduction: Periodontitis may add to the systemic inflammatory burden in individuals with chronic kidney disease (CKD), thereby contributing to an increased mortality rate. This study aimed to determine the association between periodontitis and mortality rate (all-cause and cardiovascular disease-related) in individuals with stage 3–5 CKD, hitherto referred to as “CKD”.

Methods: Survival analysis was carried out using the Third National Health and Nutrition Examination Survey (NHANES III) and linked mortality data. Cox proportional hazards regression was employed to assess the association between periodontitis and mortality, in individuals with CKD. This association was compared with the association between mortality and traditional risk factors in CKD mortality (diabetes, hypertension and smoking).

Results: Of the 13,784 participants eligible for analysis in NHANES III, 861 (6%) had CKD. The median follow-up for this cohort was 14.3 years. Adjusting for founders, the 10-year all-cause mortality rate for individuals with CKD increased from 32% (95% CI: 29–35%) to 41% (36–47%) with the addition of periodontitis. For diabetes, the 10-year all-cause mortality rate increased to 43% (38–49%).

Conclusion: There is a strong, association between periodontitis and increased mortality in individuals with CKD. Sources of chronic systemic inflammation (including periodontitis) may be important contributors to mortality in patients with CKD.

Chronic kidney disease (CKD) affects between 8 and 13% of the global population (Jha et al. 2013) and is associated with increased morbidity and mortality. Cardiovascular disease (CVD)-related events are the main cause of mortality in patients with CKD (Go et al. 2004) and systemic inflammation is recog-
ized as a non-traditional risk factor associated with increased risk of CVD events in such patients (Menon et al. 2005).

Severe periodontitis is the sixth most common human disease (Kassebaum et al. 2014) causing micro-ulceration of the investing sulcular and pocket lining epithelium of affected teeth. The estimated surface area of this ulcerated epithelium approximates 40 cm² in severe disease (Nesse et al. 2008). Consequently, individuals with periodontitis have elevated systemic markers of acute-phase (C-reactive protein/CRP, Interleukin-6/IL-6) and oxidative stress (peripheral neutrophil hyperactivity) responses. This has potential systemic consequences and co-morbid effects that have been implicated in other disease processes such as diabetes and CVD (Chapple & Genco 2013, Tonetti & VanDyke 2013).

We have reported that patients with CKD have an increase in prevalence of periodontitis compared with community dwelling adults (Sharma et al. 2014). This finding is supported by a recent systematic review, reporting an association between periodontitis and CKD in several populations with a combined odds-ratio (OR) of 1.65 (95% confidence interval/CI: 1.53–2.01) (Chambrone et al. 2013).

Successful periodontal treatment can reduce levels of systemic inflammation in patients with and without CKD (D’Aiuto et al. 2004, Vilela et al. 2011, Siribamrungwong et al. 2014, Fang et al. 2015). However, the only investigations into associations between periodontitis and mortality rates (all-cause and CVD) in patients with CKD have involved relatively small numbers of patients (ranging from 122–253 patients) on haemodialysis and with a short follow-up period (ranging from 18 months to 6 years) (Kshirsagar et al. 2009, Chen et al. 2011, de Souza et al. 2014). In epidemiological studies reporting mortality outcomes from non-CKD populations some, (Garcia et al. 1998, Xu & Lu 2011, Linden et al. 2012) but not all, (Avlund et al. 2009, Kim et al. 2013) report a significant positive association between periodontitis and an increased mortality rate.

The aim of this study was to evaluate the association between periodontitis and other traditional risk factors (diabetes, hypertension and smoking status) and mortality (all-cause and CVD) in individuals with stage 3–5 CKD, compared to those without using robust, large-scale, population-based data.

**Materials and Methods**

**Data source**

Data were derived from the Third National Health and Nutrition Examination Survey (NHANES III, 1988–1994), a representative survey of the civilian, non-institutionalized US population conducted by the National Center for Health Statistics (NCHS) of the Center for Disease Control and Prevention. Details of the survey design and methodology are available elsewhere (NCHS, 2006a). Briefly, individuals were interviewed at home, then invited to a mobile examination centre (MEC) for further interviews, tests and examinations.

**Assessment of periodontal health**

Details of the oral health component of NHANES III are published elsewhere (Drury et al. 1996). Briefly, detailed periodontal measurements were taken from volunteers aged 13 and over. The teeth were divided into two maxillary and two mandibular halves and measurements were taken from two sites per tooth (mid-buccal and mesio-buccal) for all teeth (excluding third molars) in one randomly chosen upper and lower quadrant. These measurements included periodontal probing depth (PPD), gingival recession and bleeding on probing (BOP). Clinical attachment loss (CAL) was calculated as the sum of the recession and PPD. Individuals receiving renal replacement therapy (through dialysis or kidney transplant) were excluded from periodontal examination.

Periodontitis was defined using the 2007 CDC/AAP (Centre for Disease Control and Prevention/American Academy of Periodontology) classification (Page & Eke 2007). In addition, continuous periodontal parameters were also employed such as mean PPD, mean CAL, cumulative periodontal probing depth (C-PPD), number of teeth present and proportion of sites that bled upon probing. Cumulative PPD was calculated as the sum of the maximum probing pocket depths ≥ mm of each tooth and as such is a surrogate measure of the potential extent of biofilm exposed connective tissues (Dietrich et al. 2008). Edentulous individuals were included in the analyses but formed a group distinct from individuals with periodontitis.

**Assessment of CKD**

The serum creatinine levels recorded in the NHANES III survey were recalibrated to be traceable to an isotope-derived mass spectroscopy method using the equation below (NCHS, 2006b):

\[
\text{Standardized creatinine} = (0.960 \times \text{serum creatinine}) - 0.18
\]

Age, sex, ethnicity and standardized serum creatinine were incorporated in the CKD Epidemiology Collaboration (CKD-EPI) equation to calculate estimated glomerular filtration rate (eGFR) (Levey et al. 2009). This equation improves mortality risk stratification in individuals with CKD compared with the Modification of Diet in Renal Disease (MDRD) equation (Shafi et al. 2012). Based on an eGFR<60 ml/min/1.73 m², individuals were classified as having stage 3–5 CKD, hitherto referred to as “CKD”.

Urinary albumin and creatinine levels were employed to calculate the albumin-creatinine ratio (ACR). Details of the laboratory assays can be found elsewhere (NCHS, 2006b). Albuminuria was classified as ACR<30 mg/g; ACR≥30 mg/g and <300 mg/g; and ACR≥300 mg/g.

**Assessment of traditional risk factors**

Individuals were classed as hypertensive if their mean (of three consecutive measurements) systolic blood pressure (BP) was ≥140 mmHg or mean diastolic BP was ≥90 mmHg.

Individuals were classed as diabetic by self-reporting (excluding gestational diabetes) or if their glycated haemoglobin (HbA1C) was ≥6.5%.

Individuals’ smoking status was determined from self-reporting and...
classified into current, former or never smokers (cigarettes only).

Covariate data

Data on covariates employed in the statistical analyses included information on age, sex, ethnicity (Non-Hispanic White, Non-Hispanic Black, Mexican American or Other), alcohol consumption (never, not in last year, between 0–14 drinks/week, more than 14 drinks/week) and self-reported history of previous cardiovascular events (stroke, heart attack or heart failure). Pulse pressure was calculated as the difference between the mean systolic and diastolic BP. Self-reported measures of socio-economic status (household income, marital status and educational attainment) were coded as follows. Household income (less than $20,000 or $20,000 or more); marital status (married or living as married, never married, divorced or separated or widowed); educational attainment (less than high school, high school diploma or more than high school). Body mass index (BMI) was coded as a categorical variable with BMI $<18.5$ kg/m$^2$ as underweight; $\geq 18.5$ kg/m$^2$ and $<25$ kg/m$^2$ as normal; $\geq 25$ kg/m$^2$ and $<30$ kg/m$^2$ as overweight and $\geq 30$ kg/m$^2$ as obese. Laboratory tests including serum cholesterol (total and high-density lipoprotein/HDL) were performed. Serum cholesterol levels were classified into binary variables (total serum cholesterol $\geq 24$ mg/L or $<24$ mg/L and serum HDL cholesterol $\geq 3.5$ mg/L or $>3.5$ mg/L). Physical activity was self-reported by individuals and reclassified as “recommended or more” if they reported moderate activity five or more times a week or vigorous activity three or more times a week. Physical activity was also classified as “recommended or more” if individuals reported moderate physical activity four or more times a week and vigorous activity one or more times a week or reported moderate activity three or more times a week and vigorous activity two or more times a week. Individuals’ physical activity was classified as “none” if they reported no leisure time physical activities. Individuals who reported some level of physical activity but less than recommended were classed as “less than recommended” (Beddhu et al. 2009).

Mortality data

The NCHS provide mortality data for NHANES III participants up to 31st December 2006, linked by probabilistic record matching with the National Death Index (NDI). The publicly available data set contains information on the mortality status of individuals aged 17 years or older. For individuals who are classified as “assumed deceased”, information is available on 113 underlying cause of death categories, based on the ninth and tenth revisions of the International Classification of Diseases (ICD-9 and ICD-10). CVD mortality was limited to cases where the underlying cause of death was coded between 53 and 75 (inclusive) (Anderson et al. 2001). Details of the linked mortality data have been published elsewhere (NCHS, 2010).

Statistical analyses

Analyses performed followed guidelines for NHANES III (NCHS, 1996), accounting for the complex survey design and sampling weights to yield estimates generalizable to the US population. Differences in categorical and continuous data were assessed for statistical significance using Pearson’s Chi-square, $t$-test, Fisher’s exact test and analysis of variance (ANOVA) as appropriate. Cox proportional hazards (PH) regression models were fitted to evaluate the association between periodontal status, traditional risk factors (diabetes, hypertension and smoking status) and all-cause and CVD mortality, independent of potential confounders. The fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment). The PH assumption was tested using Schoenfeld residuals, scaled Schoenfeld residuals and graphical methods. Variables were chosen to minimize missing data. Any individuals with missing covariate data were not included in the analyses (listwise deletion). Thus out of a possible 13,784 individuals eligible for analyses, 1379 (10%) individuals were excluded due to incomplete covariate data (Table S1).

We considered the effect measure modification of mortality (all-cause and cardiovascular) in individuals with CKD according to their periodontal health status. We conducted formal tests of interaction between periodontal variables and CKD case definition by entering interaction terms in the model. Further formal tests of interactions between CKD, periodontitis or edentulism and age, gender and ethnicity were also carried out.

Analyses were carried out using Stata/IC version 12.1 (StataCorp LP, College Station, TX, USA).

Results

Description of whole population and subpopulations

We analysed data from individuals in NHANES III aged 20 years and older with complete data on serum creatinine, periodontal status and mortality follow-up ($n = 13,784$) and with a median follow-up time of 14.3 years (mean 13.5 years, range 1 month–18.2 years). Of the 13,794 individuals included in the analyses, 861 (6%) were classified as CKD and 12,923 as non-CKD. Individuals with CKD were more likely to be older, have different ethnic and socio-economic mix, non-smokers (never or ex-smokers), diabetic, hypertensive, with higher total serum cholesterol and lower levels of serum HDL, report lower levels of physical activity and consume less alcohol and report a history of CVD (stroke, heart attack and congestive heart failure) compared to those without CKD. Individuals with CKD were more likely to suffer from periodontitis (or be edentulous) and have fewer teeth compared to individuals without CKD. When examining continuous variables of periodontal health, patients with CKD were more likely to have a greater mean CAL and greater BOP (Table 1).

Among individuals with CKD, those with periodontitis were more likely to be older, of non-white eth-
Table 1. Demographics of study population divided by CKD and periodontal status. Values are percentages (standard error) unless stated

| Characteristics                | No CKD (eGFR ≥ 60 ml/min/1.73 m²) | CKD (eGFR<60 ml/min/1.73 m²) | p-values* | p-values† |
|--------------------------------|-----------------------------------|-------------------------------|-----------|-----------|
|                                | Periodontitis n = 1637 (13%) | Edentulous n = 1197 (9%) | Periodontitis n = 172 (20%) | Edentulous n = 332 (39%) |       |       |
| Assumed deceased               | Healthy n = 10,089 (78%) |                                  | Healthy n = 357 (41%) |                                  |       |       |
| All-cause mortality            | 11 (0.2)                      | 35 (1.1)                      | 39 (0.9)     | 48 (1.6)     | <0.001 | <0.001 |
| Cardiovascular mortality       | 4 (0.2)                       | 14 (1.7)                      | 73 (0.6)     | 45 (3.8)     | <0.001 | 0.03   |
| Mean (SE) age (years)          | 41 (0.4)                      | 55 (0.4)                      | 54 (2.6)     | 55 (2.7)     | 0.95   | 0.07   |
| Female                         | 55 (0.4)                      | 37 (1.2)                      | 54 (1.4)     | 59 (2.7)     | <0.001 | 0.07   |
| Ethnicity                      | Non-Hispanic White            | 37 (0.5)                      | 32 (1.2)     | 60 (1.4)     | <0.001 | <0.001 |
|                                | Non-Hispanic Black            | 27 (0.4)                      | 34 (1.2)     | 23 (1.2)     | <0.001 | 0.03   |
|                                | Mexican American              | 31 (0.4)                      | 30 (1.1)     | 13 (1.0)     | <0.001 | 0.04   |
|                                | Other                          | 4 (0.2)                       | 3 (0.4)      | 4 (0.5)      | <0.001 | 0.07   |
|                                | Current Smoker                 | 24 (0.4)                      | 39 (1.2)     | 29 (1.3)     | <0.001 | 0.03   |
|                                | Diabetic                       | 6.7 (0.2)                     | 17.7 (0.9)   | 20.3 (1.2)   | <0.001 | 0.07   |
|                                | Hypertensive                   | 16 (1.3)                      | 33 (1.2)     | 44 (1.4)     | <0.001 | 0.07   |
|                                | Alcohol consumption            |                               |             |             |       |       |
|                                | Never                          | 17 (0.4)                      | 16 (0.9)     | 25 (1.3)     | <0.001 | 0.07   |
|                                | Not in last year               | 33 (0.5)                      | 40 (1.2)     | 49 (1.5)     | <0.001 | 0.07   |
|                                | 0-14 drinks/week               | 44 (0.5)                      | 36 (1.2)     | 22 (1.2)     | <0.001 | 0.07   |
|                                | >14 drinks/week                | 6 (0.2)                       | 8 (0.7)      | 4 (0.5)      | <0.001 | 0.07   |
|                                | History of stroke              | 1.1 (0.1)                     | 3.5 (0.5)    | 4.6 (0.6)    | <0.001 | 0.51   |
|                                | History of heart attack        | 1.9 (0.1)                     | 5.1 (0.5)    | 7.6 (0.8)    | <0.001 | 0.002  |
|                                | History of congestive heart failure | 1.5 (0.1)              | 3.1 (0.4)    | 5.1 (0.6)    | <0.001 | 0.53   |
|                                | Mean (SE) eGFR (ml/min/1.73 m²) | 107 (0.2)                    | 96 (0.5)     | 87 (0.4)     | <0.001 | 0.005  |
|                                | Mean (SE) ACR (mg/g)           | 19.8 (1.3)                    | 53.5 (10.0)  | 63.2 (12.5)  | <0.001 | 0.54   |
|                                | Mean (SE) BMI (kg/m²)          | 27.1 (0.06)                   | 27.6 (0.15)  | 27.0 (0.16)  | 0.27   | 0.16   |
|                                | Total serum cholesterol (≥24 mg/L) | 25 (0.4)                    | 35 (1.2)     | 44 (1.4)     | <0.001 | 0.512  |
|                                | HDL cholesterol (≥3.5 mg/L)    | 11 (0.3)                      | 17 (0.9)     | 13 (1.0)     | <0.001 | 0.767  |
|                                | Pulse pressure (mm Hg)         | 47 (0.1)                      | 56 (0.4)     | 63 (0.6)     | <0.001 | 0.002  |
| Marital status                 | Married                        | 63 (0.5)                      | 65 (1.2)     | 57 (1.4)     | <0.001 | 0.53   |
|                                | (or living as married)         |                               |             |             |       |       |
|                                | Never married                  | 21 (0.4)                      | 9 (0.7)      | 5 (0.6)      | <0.001 | 0.001  |
|                                | Divorced or separated          | 11 (0.3)                      | 13 (0.8)     | 11 (0.9)     | <0.001 | 0.001  |
|                                | Widowed                        | 5 (0.2)                       | 12 (0.8)     | 26 (1.3)     | <0.001 | 0.001  |
|                                | Household income (≥$20,000)    | 43 (0.5)                      | 57 (1.2)     | 66 (1.4)     | <0.001 | 0.004  |
| Educational status            | Less Than High School          | 33 (0.5)                      | 54 (1.2)     | 63 (1.4)     | <0.001 |       |
|                                | High School Diploma            | 33 (0.5)                      | 28 (1.1)     | 26 (1.3)     | <0.001 |       |
|                                | (including GED)                |                               |             |             |       |       |
|                                | More Than High School          | 34 (0.5)                      | 18 (1.0)     | 11 (0.9)     | <0.001 |       |
| Physical activity             | None                            | 18 (0.4)                      | 25 (1.1)     | 30 (1.3)     | <0.001 | 0.15   |
|                                | Less than recommended          | 44 (0.5)                      | 43 (1.2)     | 36 (1.4)     | <0.001 | 0.10   |
|                                | Recommended or more            | 38 (0.5)                      | 32 (1.2)     | 34 (1.4)     | <0.001 | <0.001 |
|                                | Mean (SE) Teeth Present        | 26 (0.1)                      | 21 (0.2)     | 0            | <0.001 | <0.001 |
|                                | Mean (SE) CAL (mm)             | 0.9 (0.008)                   | 3.1 (0.04)   | N/A          | <0.001 | <0.001 |
|                                | Mean (SE) PPD (mm)             | 1.5 (0.004)                   | 2.2 (0.02)   | N/A          | <0.001 | <0.001 |
|                                | Mean (SE) C-PPD (mm)           | 1.8 (0.04)                    | 11.4 (0.3)   | N/A          | <0.001 | <0.001 |
|                                | BOP                            | 11 (0.2)                      | 18 (0.5)     | N/A          | <0.001 | 0.015  |

ACR, albumin-creatinine ratio; BMI, body mass index; BOP, percentage of sites that bleed on probing; CAL, clinical attachment loss; C-PPD, cumulative probing depth; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; PPD, periodontal probing depth.

*Comparing no CKD and CKD.
†Within individuals with CKD, comparing healthy and periodontitis.

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nicity, current smokers, diabetic and hypertensive and have a lower eGFR compared to periodontally healthy individuals. These individuals also had lower household incomes and educational attainments compared to periodontally healthy individuals. Periodontally healthy individuals were similar to those with periodontitis in terms of their sex, alcohol consumption, marital status, physical activity, history of CVD events and BMI (Table 1).

All-cause mortality

After adjusting for covariates, individuals with CKD had a 44% (95% CI: 28–63%) increased rate of all-cause mortality compared to those without CKD (Table 2). Individuals with periodontitis had a 36% (22–51%) increased rate of all-cause mortality compared to individuals who were periodontally healthy.

The association between periodontitis and all-cause mortality was similar between individuals with or without CKD (p-value for interaction = 0.57). Similarly, the associations between CKD and all-cause mortality did not vary by age, sex or diabetes status (p-values for interaction 0.14, 0.99 and 0.09 respectively). Furthermore, the association between periodontitis and all-cause mortality did not vary by age, gender or diabetes status (p-values for interaction 0.73, 0.51 and 0.51 respectively). In edentulous individuals, there was a significant difference in all-cause mortality by age. Edentulous individuals under the age of 65 had a significantly increased rate of all-cause mortality compared to edentulous individuals 65 years and older, hazard ratio (HR) 1.85 (1.41–2.44) and 1.18 (1.04–1.33) respectively (Tables S2, S3 and Fig. S1).

For continuous measures of periodontitis in fully adjusted models, an increased mortality rate was seen with worsening periodontal health in a dose-dependent manner. For example a 1 mm increase in mean PPD was associated with a 17% (6–28%) increase in incident rate of all-cause mortality (Table 2). Edentulousness was associated with a 32% (17–50%) increased rate of all-cause mortality compared with periodontally healthy dentate individuals.

Diabetes (HR 1.41; 1.27–1.57), hypertension (HR 1.06; 0.93–1.20) and current smoking (HR 2.12; 1.82–2.48) were associated with an increased rate of all-cause mortality although this increase was not significant for hypertension (Table 2).

Table 2. Results from Cox proportional hazards regression analyses for all-cause and cardiovascular mortality using an age and sex-adjusted and a fully adjusted model

| Hazard Ratio (95% CI) of All-cause mortality | Hazard Ratio (95% CI) of Cardiovascular mortality |
|---------------------------------------------|-------------------------------------------------|
| CKD                                         |                                                 |
| Periostal status                            |                                                 |
| Healthy                                     | 1.0 (Ref)                                       |
| Periodontitis                               | 1.78 (1.59–2.00)                               |
| Edentulous                                  | 1.83 (1.64–2.05)                               |
| Mean PPD (per mm)                           | 1.48 (1.35–1.62)                               |
| Mean CAL (per mm)                           | 1.20 (1.16–1.25)                               |
| C-PPD (per 10 mm)                           | 1.29 (1.20–1.38)                               |
| BOP (per 10%)                               | 1.10 (1.07–1.13)                               |
| Diabetes                                    | 1.85 (1.63–2.10)                               |
| Hypertension                                | 1.28 (1.15–1.43)                               |
| Smoking status                              | 1.0 (Ref)                                       |
| Former                                      | 1.41 (1.23–1.60)                               |
| Current                                     | 2.70 (2.35–3.09)                               |

BOP, proportion of sites that bleed on probing; CAL, clinical attachment loss; CKD, chronic kidney disease; C-PPD, cumulative periodontal probing depth; PPD, periodontal probing depth.

Fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment).

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mortality was similar between individuals with or without CKD (p-value for interaction = 0.27). The associations between CKD and CVD mortality did not vary by age, sex or diabetes status (p-values for interaction 0.39, 0.82 and 0.34 respectively). The association between periodontitis and CVD mortality did not vary by gender or diabetes status (p-values for interaction 0.77 and 0.17 respectively). There was a trend in patients with CKD and periodontitis to have an increased HR of CVD mortality if they were under the age of 65 compared with 65 and over but this was not significant. In edentulous individuals, there was a significant difference in CVD mortality by age. Edentulous individuals under the age of 65 having a significantly increased rate of CVD mortality, HR 2.03 (1.31–3.13), compared to edentulous individuals 65 years and older who had comparable rates of CVD mortality compared to periodontally healthy individuals, HR 0.89 (0.71–1.10) (Tables S4, S5 and Fig. S2).

For continuous measures of periodontal health, mean PPD and percentage of sites that bleed on probing were associated with a statistically significant increase in the rate of CVD mortality (Table 2). Edentulous and periodontally healthy dentate individuals had comparable rates of CVD mortality (Table 2).

Diabetes (HR 1.45; 1.24–1.70), hypertension (HR 1.32; 1.06–1.63) and current smoking (HR 2.10; 1.69–2.62) were associated with an increased rate of CVD mortality (Table 2).

The 10-year CVD mortality for individuals with CKD (and combinations of risk factors) highlights the similarity in the magnitude of increase in CVD mortality associated with diabetes (24%; 19–30%) compared with periodontitis (22%; 19–27%) (Table 4). Estimated CVD survival for individuals with CKD and

Table 3. Ten-year all-cause mortality (percentages) of individuals with CKD by risk factors (along with the addition of periodontitis to the risk factor)

| Risk factor | 10-year all-cause mortality (95% CI) without periodontitis | 10-year all-cause mortality (95% CI) with periodontitis |
|-------------|------------------------------------------------------------|--------------------------------------------------------|
| CKD         | 32% (29–35%)                                               | 41% (36–47%)                                           |
| CKD + Diabetes | 43% (38–49%)                                           | 55% (47–63%)                                           |
| CKD + Hypertension | 34% (29–39%)                                      | 44% (37–52%)                                           |
| CKD + Smoking | 58% (51–65%)                                            | 71% (62–79%)                                           |

Fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment).

Fig. 1. For all-cause mortality. Cox proportional hazard regression graphs (adjusting for age, sex, ethnicity, pulse pressure, history of CVD, alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity, household income, marital status and educational attainment) of survival in patients with CKD stratified using periodontitis and other traditional risk factors (diabetes, hypertension and smoking). The reference lines indicate 10 year survival.

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different risk factor profiles is given in Fig. 2.

Discussion
In this large cohort, representative of the US population from which it was derived, CKD was associated with increased rates of all-cause mortality and CVD mortality, independent of periodontitis, traditional risk factors and other confounders. Periodontitis was associated with increased rates of all-cause and CVD mortality comparable with, but independent of, that associated with diabetes (Tables 2–4; Figs 1 and 2). There was an increased rate of all-cause mortality but not CVD mortality in edentulous individuals with CKD compared with periodontally healthy dentate individuals. The association between edentulousness and CVD mortality was significant in a subgroup of edentulous individuals under the age of 65. Given the high prevalence of chronic periodontitis in patients with CKD (Chambrone et al. 2013), our results suggest that periodontitis may be an important non-traditional risk factor for CVD and all-cause mortality in these patients, and interestingly contributing to the increased risk to a similar extent as diabetes.

The strengths of this study are its large population-based sampling with robust sampling methodology which allow the results from this analysis to be generalized to the US population. The detailed clinical, demographic and anthropomorphic data collected allows for many of the known covariates to be accounted for in the Cox proportional hazards regression model, generating more accurate point estimates. The length of follow-up for this study is its final strength and allows for the pragmatic assessment of long term, hard outcomes (all-cause and CVD mortality). The

Table 4. Ten-year CVD mortality (percentages) of individuals with CKD by risk factors (along with the addition of periodontitis to the risk factor)

| Risk factor       | 10-year CVD mortality (95% CI) without periodontitis | 10-year CVD mortality (95% CI) with periodontitis |
|-------------------|------------------------------------------------------|--------------------------------------------------|
| CKD               | 16% (14–19%)                                         | 22% (19–27%)                                     |
| CKD + Diabetes    | 24% (19–30%)                                         | 32% (27–39%)                                     |
| CKD + Hypertension| 21% (16–28%)                                         | 29% (22–37%)                                     |
| CKD + Smoking     | 33% (24–44%)                                         | 43% (32–56%)                                     |

Fully adjusted model adjusted for age, sex, ethnicity, CKD status, periodontal status, diabetic status, hypertensive status, smoking status, pulse pressure, history of CVD (heart attack or stroke or heart failure), alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity and measures of socio-economic status (household income, marital status and educational attainment).

Fig. 2. For cardiovascular mortality. Cox proportional hazard regression graphs (adjusting for age, sex, ethnicity, pulse pressure, history of CVD, alcohol consumption, ACR, hypercholesterolaemia and low-HDL, BMI, physical activity, household income, marital status and educational attainment) of survival in patients with CKD stratified using periodontitis and other traditional risk factors (diabetes, hypertension and smoking). The reference lines indicate 10-year survival.
from the small sample sizes (122
2011, de Souza et al. 2014). Apart
(Kshirsagar et al. 2009, Chen et al.
odontitis in patients with CKD have
link between mortality and peri-
cannot be ruled out. Variables not included in the analysis
of variables or confounding from
rate measurement or categorization
of residual confounding from inaccu-
rate measurement or categorization
of variables or confounding from
variables not included in the analysis
cannot be ruled out.

Previous studies investigating the
link between mortality and peri-
donitis in patients with CKD have
done so in patients on haemodialysis
(Kshirsagar et al. 2009, Chen et al.
2011, de Souza et al. 2014). Apart
from the small sample sizes (122–253
patients) and shorter follow-up pe-
riod (18 months to 6 years), these
studies differed significantly from the
present analysis as individuals receiv-
ing RRT (through chronic dialysis or a functioning kidney transplant)
were not included in the present
analysis (RRT was an exclusion cri-
teria for periodontal examination
in NHANES III). Hence, even though
these studies demonstrate an associ-
ation between periodontitis and mor-
tality, thereby lending support to the
current findings, the results cannot
be directly compared.

A putative mechanism for a pos-
sible link between periodontitis and
increased all-cause and CVD mortal-
ity is via the increased systemic
acute-phase and oxidative stress bur-
den. This increased burden is seen in
individuals with periodontitis and
CKD (Ioannidou et al. 2011) and
individuals with periodontitis who
do not have CKD (D’Aiuto et al.
2004, Chapelle & Genco 2013). Increased systemic inflammatory and
oxidative stress burdens increase the
incidence of CVD events in patients
with CKD (Arici & Walls 2001,
Mathew et al. 2008, Li et al. 2015).
This mechanism is supported by the
association demonstrated here
between increased risk of CVD mor-
tality and measures of active peri-
donitis (periodontitis case
definition, mean PPD and BOP), as
opposed to measures of historical
periodontitis (edentulousness and
mean CAL), where there was a lack
of association (Table 2). However,
at least part of the association between
periodontitis and CVD may also be
due to common risk factors such as
smoking and diabetes (Dietrich et al.
2008, Mucci et al. 2009). The
increase in all-cause mortality in
dentulous individuals compared to
periodontally healthy dentate indi-
viduals, as reported here and also by
other investigators in non-CKD
cohorts (Brown 2009), may be due
to several factors. Patients are ren-
dered edentulous for a variety of
reasons including periodontitis, with
approximately 50% of teeth being
extracted due to periodontal disease
(Phipps & Stevens 1995). As approx-
imately half of all tooth extractions
are for reasons other than periodon-
tal disease, edentulousness may act
as a surrogate marker of general
health attitudes and/or behaviours,
limited healthcare access or other
socio-economic measures (Joshipura
& Ritchie 2005). This might also
explain the association between
dentulousness and CVD mortality
in patients under the age of 65 who
might have such characteristics and
attitudes towards healthcare that
render them edentulous before the
age of 65.

The biological mechanisms
underpinning the relationship
between periodontitis and increased
mortality in individuals with CKD
form a promising area of research
and may produce mechanistic targets
leading to risk stratification and
novel interventions. Ongoing longi-
tudinal studies (Stringer et al. 2013)
investigating large cohorts of
patients with pre-dialysis CKD may
provide confirmation of this associa-
tion and shed light upon explanatory
mechanisms. Successful treatment of
periodontitis has been shown to
improve surrogate markers of CVD
risk, including serum markers of sys-
temic inflammation (CRP, IL-6)
(D’Aiuto et al. 2004), endothelial
function as measured by flow-
mediated dilatation (FMD) and
endothelial-activation markers such
as soluble E-selectin and von Wille-
brand factor (Tonetti et al. 2007).
Two randomized controlled trials of
periodontal interventions in patients
with CKD have been carried out but
limited to cohorts of haemodialysis
patients. These have produced con-
flicting results either not demonstrat-
ing changes in inflammatory markers
following periodontal intervention
(Wehmeyer et al. 2013) or demon-
strating that significant reductions in
inflammatory markers can be achieved
following periodontal ther-
apy (Fang et al. 2015). Currently,
patients with CKD are managed to
strict targets concerning glycaemic
control (diabetes) and control of
hypertension and smoking cessation
to improve outcomes. If a causal
link is established between periodon-
titis and increased rates of adverse
outcomes in CKD patients, then
establishing and maintaining peri-
donatal health may become an
important part of the care pathway
of patients with CKD.

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**Supporting Information**

Additional Supporting Information may be found in the online version of this article:

**Figure S1** Cox PH regression graphs for all-cause mortality in individuals with periodontitis/edentulism and CKD by age category

**Figure S2** Cox PH regression graphs for CVD mortality in individuals with periodontitis/edentulism and CKD by age category.

**Table S1** Numbers of participants (and percentage) with missing data in variables included in statistical model.

**Table S2** Exploring the interactions between CKD (stage 3–5), periodontal variables and age, gender and diabetes status for all-cause mortality.

**Table S3** Hazard ratios (95% CI) and 10-year survival (95% CI) of all-cause mortality by subgroups of age (<65 years of age and ≥65 years of age).

**Table S4** Exploring the interactions between CKD (stage 3–5), periodontal variables and age, gender and diabetes status for CVD mortality.

**Table S5** Hazard ratios (95% CI) and 10-year survival (95% CI) of CVD mortality by subgroups of age (<65 years of age and ≥65 years of age).

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**Clinical Relevance**

*Scientific rationale for the study: CKD prevalence and complications cannot be entirely explained by traditional risk factors such as diabetes or cardiovascular disease (CVD). Periodontitis is independently associated with CKD and contributes to the systemic inflammatory burden, therefore this study aimed to establish the association between periodontitis and mortality in patients with chronic kidney disease (CKD).*

*Principal findings: Periodontitis was associated with a 9% (absolute) or 28% (relative) increase in all-cause mortality at 10 years for individuals with CKD, within the limitation of this analysis. This association is of a similar magnitude, but independent of, that seen between diabetes and mortality in individuals with CKD.*

*Practical implications: Periodontitis may be an important predictor of mortality in patients with CKD and sources of chronic inflammation (including periodontitis) may be important contributors beyond traditional risk factors in patients with CKD.*