E. Ioannidou^{1*}, H. Swede²,
and A. Dongari-Bagtzoglou¹

¹Division of Periodontology, Department of Oral Health and Diagnostic Sciences; and ²Division of Epidemiology and Biostatistics, Department of Community Medicine and Health Care, University of Connecticut Health Center, 263 Farmington Ave., Farmington, CT 06030, USA; *corresponding author, ioannidou@uchc.edu

J Dent Res 90(12):1411-1415, 2011

ABSTRACT

Based on the existing evidence supporting a state of chronic inflammation in chronic kidney disease (CKD), we hypothesized that periodontal infection may affect the systemic inflammatory status of a nationally representative CKD population as measured by serum C-reactive protein (CRP). We examined this hypothesis using the National Health and Nutrition Examination Survey 1988-1994 (NHANES III) dataset including 2303 individuals. We followed the American Academy of Periodontology (AAP)/Centers for Disease Control and Prevention (CDC) case definition for periodontitis. We used a cutoff point of 30% sites with (PD) ≥ 5 mm and (CAL) ≥ 4 mm to define generalized periodontitis cases. We estimated glomerular filtration rate based on cystatin C levels using the relevant equation. Urinary albumin-to-creatinine ratio was calculated in milligrams *per* gram with a cutoff point of 30 mg/g. CKD was defined based on eGFR < 60 mL/min/1.73m² and albuminuria ≥ 30 mg/g. Periodontitis was found in 427 (12.3%) individuals. Of individuals with periodontitis, 41.8% had serum CRP higher than 0.3 mg/dL compared with 27.1% of non-periodontitis and 53.1% of edentulous individuals ($p = 0.001$ for all comparisons). When the extent of periodontitis was used as one of the independent variables, the parsimonious model showed a strong independent association between extent of periodontitis and serum CRP levels (OR = 2.0, CI95% = 1.2-3.6).

KEY WORDS: NHANES, periodontitis, chronic kidney disease, C-reactive protein, epidemiology, inflammation.

DOI: 10.1177/0022034511423394

Received June 2, 2011; Last revision August 15, 2011; Accepted August 20, 2011

© International & American Associations for Dental Research

Periodontitis Predicts Elevated C-reactive Protein Levels in Chronic Kidney Disease

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide public health problem with rising prevalence and poor outcomes (Levey *et al.*, 2011). It has been estimated that approximately 25 million in the United States may have CKD (Coreshet *et al.*, 2007). Elevated levels of inflammatory markers such as CRP and IL-6 are known predictors of cardiovascular outcomes in the general population as well as in the CKD population, where they are linked to malnutrition and increased mortality (Stenvinkel, 2001).

There are several different mechanisms that have been proposed in the literature to explain the high inflammatory status in this population, including the deterioration of renal function, leading to low urinary IL-6 excretion and triggering increased serum cytokine levels (Herbelin *et al.*, 1991), overproduction of pro-inflammatory cytokines caused by an elevated number of circulating monocytes (Girndt *et al.*, 1998), increased oxidative stress (Himmelfarb *et al.*, 2002), the accumulation of advanced glycation end-products (AGEs) caused by decreased renal clearance (Busch *et al.*, 2010), which can trigger an inflammatory response (Schwedler *et al.*, 2001), and the presence of co-morbid factors such as diabetes (Stenvinkel, 2001).

There is evidence supporting the contribution of periodontitis to systemic inflammation (Ebersole and Cappelli, 2000). Several possible mechanisms have been suggested, including the locally produced inflammatory mediators that are introduced to systemic circulation as well as bacterial by-products that invade the blood stream, interact with host cells, and trigger inflammatory response (Ebersole and Cappelli, 2000).

Based on the above evidence supporting a state of chronic inflammation in CKD (Stenvinkel *et al.*, 2001), we hypothesized that periodontal infection may contribute to the systemic inflammatory burden. This hypothesis was examined for the first time in a large, representative CKD sample of the US population by the National Health and Nutrition Examination Survey 1988 to 1994 (NHANES III).

MATERIALS & METHODS

Study Population

NHANES, a periodic survey conducted by the Centers for Disease Control and Prevention (CDC), provides national estimates of health and nutritional status of the civilian, non-institutionalized population (CDC, 2011). Individuals participated in interviews conducted at home and in extensive physical examinations, performed at an examination center, which included blood and urine collection. Our study population consisted of CKD individuals who were 21 yrs of age and older, and were dentate (≥ 2 teeth), to apply

the selected definition for moderate periodontitis. Furthermore, we performed a comparative analysis in a subset of completely edentulous CKD individuals.

Information on age, sex, race, and smoking history was based on self-report during the survey interview. We constructed a binary age variable using a cutoff point of 60 yrs based on risk assessment for CKD (Levey *et al.*, 2011). Smoking status was determined from the answers to the questions: "Have you smoked at least 100 cigarettes in your life?" and "Do you smoke cigarettes?" Additionally, diabetes was defined based on the answer to the question: "Have you been told by your doctor that you have diabetes?" Glycated hemoglobin was used as an indicator of diabetes control with a cutoff of 7% (ADA, 2011). We constructed a variable for diabetes duration using a previously used cutoff point of 10 yrs (Fisher *et al.*, 2008). History of cardiovascular disease (CVD) was constructed as a variable derived from the self-reported history of heart attack, stroke, heart failure, and hypertension (Kshirsagar *et al.*, 2008). Education and income variables were constructed as reported previously (Ioannidou and Swede, 2011), whereas Body Mass Index (BMI) was calculated as body weight (kg) divided by squared height (m^2) and was stratified into 4 standard categories.

Periodontitis Definition

For NHANES III, the partial mouth periodontal examination (PMPE) was conducted at 2 sites *per* tooth in 2 randomly chosen quadrants. All third molars were excluded. We followed the American Academy of Periodontology (AAP)/CDC definition for moderate periodontitis and used at least 2 interproximal sites with clinical attachment loss (CAL) ≥ 4 mm not on the same tooth, or at least 2 sites with probing depth (PD) ≥ 5 mm not on the same tooth (Page and Eke, 2007).

Additionally, we constructed a variable representing the extent of periodontitis as a function of the percentage of interproximal sites with (PD) ≥ 5 mm and (CAL) ≥ 4 mm. We used a cutoff point of 30% sites with (PD) ≥ 5 mm and (CAL) ≥ 4 mm to characterize generalized periodontitis cases based on the Consensus Report by the AAP (Lindhe *et al.*, 1999). As a result, any case with more than 30% sites with (PD) ≥ 5 mm and (CAL) ≥ 4 mm in the 2 examined quadrants was considered a generalized periodontitis case. The non-periodontitis or localized periodontitis group [0%-30% sites with (PD) ≥ 5 mm and (CAL) ≥ 4 mm] was used as the referent group.

Kidney Function

Estimated glomerular filtration rate (eGFR) based on cystatin C levels has been shown to be independent of age and race, contrary to estimated GFR based on serum creatinine levels (Stevens *et al.*, 2008). Thus, we estimated GFR based on cystatin C levels using the equation: $76.7 \times \text{Cystatin C}^{-1.19}$ (Stevens *et al.*, 2008). Estimated GFR is reported in mL/min/1.73 m^2 . Urinary albumin-to-creatinine ratio (albuminuria) was calculated in milligrams *per* gram, with a cutoff point of 30 mg/g (Coresh *et al.*, 2007). We defined CKD based on the recent classification that combined eGFR values < 60 mL/min/1.73 m^2 and albuminuria ≥ 30 mg/g (Levey *et al.*, 2011).

All eGFR values above 200 mL/min/1.73 m^2 were truncated at that level (Coresh *et al.*, 2007). All individuals with eGFR < 15 mL/min/1.73 m^2 were excluded, due to likelihood of their being on dialysis or seriously ill with low response rate. Cutoff points for CKD stages followed the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (Levey *et al.*, 2011).

Serum CRP Levels

We constructed a dichotomous variable representing serum CRP levels with a cutoff point of 0.3 mg/dL based on the current guidelines for CRP predictive value among individuals with a history of CVD (Pearson *et al.*, 2003).

Statistical Analyses

Analyses were performed with Predictive Analytics Software (PASW) Version 18 with Complex Sample Module incorporating sampling weights in the NHANES dataset (Mohadjer *et al.*, 1996). Categorical variables were tested with the Pearson chi-square test, and continuous variables were tested with the *t* test for independent samples. We performed binary logistic regression to calculate crude and adjusted Odds Ratios (OR) and 95% Confidence Intervals (CI) for periodontitis among CKD cases. We used a non-automated stepwise regression modeling to assess the association of periodontitis with serum CRP. We added, in sequence, relevant confounders to produce the full model. Any confounder with a $p > 0.1$ in the Wald F statistics was excluded from the parsimonious model. Four logistic regression analyses were applied in the dentate population: Crude model—unadjusted; Model 1—age, sex, and race; Model 2—based on previous evidence (Coresh *et al.*, 2007; Kshirsagar *et al.*, 2008) and fully adjusted for age, sex, race, diabetic control and duration, BMI, smoking, antihyperlipidemic medication, antibiotic and antiviral medication, cardiovascular disease history, education, and income; Model 3 (full model)—based on the previous model and CKD status based on reduced eGFR and albuminuria; and Model 4—parsimonious model. P-values of < 0.05 were accepted as statistically significant in all analyses.

RESULTS

Of the total NHANES III study population (39,695), there were 2155 individuals who fulfilled the CKD inclusion criteria, having either albuminuria or eGFR < 60 mL/min/1.73 m^2 . The addition of 148 edentulous CKD individuals resulted in a total population of 2303. Descriptive characteristics of the study sample stratified by oral health status are presented in Table 1.

Among the dentate individuals, 427 (12.3%) were diagnosed with periodontitis. Of these, 24.3% were non-Hispanic Black compared with 14.5% in the non-periodontitis group and 11.7% in the edentulous group. CKD cases with periodontitis had significantly higher prevalence of diabetes, or poor diabetic control for longer time periods (Table 1). Furthermore, the distribution of the population *per* CKD stage and presence or absence of albuminuria (Table 1) revealed that most individuals with periodontitis combined reduced eGFR and albuminuria. Of the

Table 1. Clinicopathological Characteristics of the CKD Population Stratified by Oral Health Status

Variables (%)	Edentulous N = 148	Periodontitis N = 427	Non-periodontitis N = 1728	P-Value
Demographic				
Age				
60+ (yrs, n = 886)	81.7 (5.1)	42.7 (3.7)	19.8 (1.2)	0.001
Race				
Non-Hispanic White (n = 1584)	86.7 (2.7)	71.3 (3.0)	83.9 (1.1)	0.001
Non-Hispanic Black (n = 655)	11.7 (2.3)	24.3 (2.4)	12.0 (0.7)	
Other (n = 64)	1.6 (1.4)	4.2 (0.8)	4.1 (2.1)	
Sex				
Female (n = 1210)	55.8 (5.7)	41.7 (3.8)	58.1 (1.8)	0.120
Medical				
Body Mass Index				
Low < 18.5 (n = 61)	7.3 (3.0)	3.6 (1.4)	2.3 (0.5)	0.018
Normal (18.5-24.9) (n = 766)	36.8 (5.5)	29.1 (3.3)	41.7 (1.9)	
Overweight (25.0-29.9) (n = 785)	24.3 (4.5)	35.4 (3.7)	32.4 (1.8)	
Obese (30.0-34.9) (n = 408)	17.2 (4.8)	17.8 (0.6)	13.0 (1.1)	
Morbidly Obese (35+) (n = 277)	14.4 (4.9)	14.1 (3.1)	10.6 (1.1)	
Diabetes (n = 358)	21.9 (4.3)	12.9 (2.3)	8.4 (0.9)	0.044
Diabetic Duration (%)				
≥ 10 yrs (n = 152)	56.4 (5.3)	43.2 (9.7)	28.2 (4.5)	0.080
Diabetic Control (%)				
HbA1c ≥ 7% (n = 280)	11.0 (4.1)	13.4 (2.4)	7.4 (0.9)	0.028
CKD Stage 1 and albuminuria (n = 1118)	68.2 (5.4)	46.6 (3.8)	39.1 (1.8)	0.070
CKD Stage 2 and albuminuria (n = 268)	7.9 (2.2)	14.2 (2.6)	8.9 (1.0)	
CKD Stage 3 and no albuminuria (n = 756)	13.9 (4.2)	33.0 (3.8)	44.1 (1.9)	
CKD Stage 3 and albuminuria (n = 85)	9.3 (3.7)	2.4 (0.9)	3.6 (0.7)	
CKD Stage 4 and no albuminuria (n = 64)	0.6 (0.6)	3.1 (1.4)	3.4 (0.6)	
CKD Stage 4 and albuminuria (n = 12)	0.1 (0.1)	0.6 (0.4)	0.8 (0.3)	
Hypertension (n = 209)	6.3 (2.4)	14.1 (0.7)	32.1 (2.8)	0.001
CVD (n = 303)	36.5 (3.5)	12.3 (0.5)	5.5 (1.7)	0.001
Smoking Status				
Current (n = 566)	32.5 (5.9)	41.8 (3.9)	24.5 (1.6)	0.001
Past (n = 627)	29.5 (5.2)	30.3 (3.6)	26.8 (1.7)	
Never (n = 1110)	37.9 (5.4)	27.9 (3.3)	48.7 (1.9)	
NSAID (n = 147)	6.3 (3.4)	6.0 (0.9)	8.8 (2.3)	0.448
Antihyperlipidemic Medication (n = 23)	0.0 (0.0)	1.3 (0.4)	0.0 (0.0)	0.001
Antibiotic, Antifungal, Antiviral Medication (n = 268)	10.2 (3.5)	10.4 (1.1)	12.2 (2.7)	0.767
Hematologic and Biochemical				
Segmented Neutrophils (n = 450)				
< 65%	65.5 (8.8)	69.4 (6.5)	66.9 (3.7)	0.921
Cholesterol Levels (n = 1252)				
≥ 200 mg/dL	73.4 (4.5)	68.2 (3.5)	49.6 (1.9)	0.0001
LDL (n = 217)				
≥ 100 mg/dL	5.7 (2.5)	5.1 (1.4)	11.3 (1.3)	0.008
C-Reactive Protein (n = 720)				
≥ 0.3 mg/dL	53.1 (6.2)	41.8 (3.7)	27.1 (1.9)	0.001
Socio-economic Status				
Education (n = 993)				
< 12 yrs	55.7 (5.9)	39.9 (3.7)	19.6 (1.3)	0.001
Perception of Health (n = 722)				
Fair-Poor	50.5 (5.8)	32.0 (3.4)	14.0 (1.0)	0.0001
Income				
Low (n = 1003)	76.2 (5.1)	41.7 (3.9)	31.3 (1.7)	
Medium (n = 770)	21.5 (5.0)	45.4 (4.2)	44.6 (1.9)	
High (n = 268)	2.3 (1.1)	12.9 (2.8)	24.1 (1.8)	0.005

individuals in the periodontitis group, 41.8% were current smokers, compared with 24.5% of the non-periodontitis and 32.5% of the edentulous individuals ($p = 0.001$ among groups). Among dentate individuals and in terms of socio-economic status, those with periodontitis showed a trend toward less education, fair-poor health perception, and medium to low income.

Based on the cutoff point of 0.3 mg/dL, 41.8% of individuals with periodontitis had high serum CRP compared with 27.1% of non-periodontitis and 53.1% of edentulous individuals ($p = 0.001$ for all comparisons).

Of the edentulous individuals, 81.7% were more than 60 yrs old compared with 42.7% and 19.8% of the periodontitis and

Table 2. Logistic Regression Models with Serum CRP as the Dependent Variable

Variables	Crude	Model 1	Model 2	Model 3	Model 4
OR (CI 95%)					
Periodontitis: Yes	1.60 (1.11-2.31)	1.53 (1.04-2.25)	1.34 (0.89-2.02)	1.19 (0.77-1.82)	1.18 (0.81-1.73)
Extent of Periodontitis $\geq$ 30% sites	1.64 (1.11-2.43)	1.60 (1.04-2.49)	1.86 (1.04-3.34)	2.01 (1.19-3.61)	2.03 (1.21-3.66)

Crude model—unadjusted; Model 1—age, sex and race; Model 2—age, sex, race, diabetic control and duration, BMI, smoking, antihyperlipidemic medication, antibiotic and antiviral medication, CVD history, education, and income; Model 3 (full model)—all previous variables plus CKD stages; and Model 4—parsimonious model.

non-periodontitis individuals, respectively ($p = 0.001$). Of the edentulous individuals, 68.2% were at CKD stage 1 with albuminuria compared with 46.6% of the periodontitis and 39.1% of the non-periodontitis individuals. Overall, the majority of the edentulous individuals (85.5%) were characterized by albuminuria regardless of the CKD stage (Table 1). In the edentulous group, 36.5% had a history of CVD compared with 12.3% of those with periodontitis and 5.5% in the non-periodontitis group ($p = 0.001$ for all comparisons). Of the edentulous individuals, 21.9% were diabetic, and 56.4% of these had diabetes duration of more than 10 yrs. In terms of SES, 55.7% of the edentulous individuals had fewer than 12 yrs of education, and 76.2% had low income (Table 1).

When periodontitis was used as one of the predictor variables and serum CRP as a dependent variable, the multivariate model 1 revealed a statistically significant association that lost significance in models 2 and 3 (full model) and the parsimonious models (model 4) (Table 2).

When the extent of periodontitis was used as one of the predictor variables and serum CRP as a dependent variable, the multivariate models 1 and 2 showed a statistically significant association (Table 2). In the full model (model 3), and after CKD status adjustment, extent of periodontitis sustained statistical significance (OR = 2.01, CI95% = 1.04-3.01). As a result of the full model, sex, race, diabetic control, BMI, smoking, and CVD and CKD status remained significant and were included in the parsimonious model (Table 2). The parsimonious model (model 4) showed an independent association between extent of periodontitis and serum CRP levels (OR = 2.03, CI95% = 1.21-3.66).

DISCUSSION

We have produced evidence consistent with our hypothesis that, in individuals with CKD, periodontitis made a significant contribution to the systemic inflammatory burden as measured by serum CRP levels. More importantly, and for the first time, we showed that generalized periodontitis was an independent predictor of elevated serum CRP levels in a nationally representative CKD sample after adjustment for significant confounders including CKD status in the most parsimonious regression model.

When data from edentulous individuals with CKD were analyzed, we showed that this population was characterized by elevated CRP levels, as was previously published (Slade *et al.*, 2000; Fisher *et al.*, 2011). Although there is a degree of periodontitis contribution to edentulism, the inflammatory burden in the edentulous population cannot be attributed to

periodontitis. Elevated CRP levels were well-anticipated due to several CRP risk factors, such as older age, prolonged diabetes, high prevalence of albuminuria, and CVD, as well as low SES, as we and others have demonstrated in this population (Slade *et al.*, 2000). Therefore, direct association of edentulism with periodontitis would have been a “liberal” assumption, which would have introduced methodology bias to the hypothesis testing.

Previous work has shown that elevated serum levels of IL-6 and CRP were present in individuals with severe periodontal disease (Ebersole and Cappelli, 2000). Also, our group has reported a dramatic elevation of IL-6 synthesis by cells within the gingival connective tissue in chronic periodontitis lesions of systemically healthy and immunocompromised patients, possibly linked to these systemic effects (Dongari-Bagtzoglou and Ebersole, 1998; Ioannidou *et al.*, 2006).

Although there is epidemiological evidence supporting the role of periodontitis as a predictor of acute phase response, as measured by serum CRP levels in the general population (Slade *et al.*, 2000; Fisher *et al.*, 2008), until now this hypothesis was never tested in a nationally representative CKD population based on NHANES III data. Non-traditional risk factors have been supported in a qualitatively and quantitatively different risk relationship with CVD in the CKD population (Sarnak, 2003). The role of systemic inflammation as a predictor of CVD mortality in individuals with CKD has been well-recognized (Sarnak, 2003). Given the well-established relationship between CVD and periodontal inflammation (Friedewald *et al.*, 2009), and our finding in this study of elevated CVD prevalence in individuals with CKD and periodontitis, persistent periodontal inflammation may be another missing link that could explain the tremendous burden of CVD in CKD.

Although our study confirms some of the findings in previously published community-based studies, it also offers several important methodological advancements over previously published work. First, compared with previous studies (Kshirsagar *et al.*, 2005; Fisher *et al.*, 2008), we used a more recent periodontitis case definition (Page and Eke, 2007), which has been adopted in official US public health publications on the national prevalence of periodontitis (Dye *et al.*, 2007). This is important, since we have shown previously that the choice of periodontitis case definition affects associations with renal function (Ioannidou and Swede, 2011). Second, we estimated GFR based on cystatin C levels, which have been shown to provide more accurate estimates compared with creatinine, which depends heavily on muscle mass, age, sex, and race (Stevens *et al.*, 2008). To eliminate these additional covariates, cystatin C, a protein that is freely filtered by the glomerulus, has been successfully used for GRF estimation (Stevens *et al.*, 2008).

Furthermore, we defined CKD based on the recent classification that combined eGFR values < 60 mL/min/1.73 m² and albuminuria ≥ 30 mg/g (Levey *et al.*, 2011) and offered an improved tool for risk prediction and prognosis assessment in CKD. Finally, we designed full regression models incorporating meaningful combinations of all potential covariates for elevated CRP levels based on existing evidence (Kshirsagar *et al.*, 2008; Upadhyay *et al.*, 2011).

As with all retrospective database-based studies, the main limitation of our study was the cross-sectional design, which prevented the assessment of temporal or causal relationships. Long-term prospective studies are needed to assess the causality of the association between periodontitis and systemic inflammation in the CKD population. An additional limitation of the NHANES periodontal protocol was the use of partial-mouth periodontal examination, which has been shown to underestimate disease prevalence (Eke *et al.*, 2010).

On the basis of our previous work (Ioannidou and Swede, 2011), an estimated 5.8 ± 0.3 million US dentate adults with CKD stages 2-4 have periodontitis, which, if untreated, may significantly affect the inflammatory status of this population. Further interventional studies are needed to test the effect of periodontal treatment on inflammatory status and cardiovascular mortality in the CKD population.

ACKNOWLEDGMENTS

This study was supported by NIH/NIDCR Research grant K23DE018689 awarded to E. Ioannidou. This research was also supported by a General Clinical Research Center grant from NIH (M01RR06192) awarded to UCHC. The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

REFERENCES

- American Diabetes Association (2011). Executive summary: standards of medical care in diabetes—2011. *Diabetes Care* 34(Suppl 1):4-10.
- Busch M, Franke S, Ruster C, Wolf G (2010). Advanced glycation end-products and the kidney. *Eur J Clin Invest* 40:742-755.
- CDC (2011). National Health and Nutrition Examination Survey (NHANES III). Analytic and reporting guidelines (1988-94). Hyattsville, MD: National Center for Health Statistics, Centers for Disease Control and Prevention. URL accessed August 23, 2011 at: <http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm>.
- Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, *et al.* (2007). Prevalence of chronic kidney disease in the United States. *J Am Med Assoc* 298:2038-2047.
- Dongari-Bagtzoglou AI, Ebersole JL (1998). Increased presence of interleukin-6 (IL-6) and IL-8 secreting fibroblast subpopulations in adult periodontitis. *J Periodontol* 69:899-910.
- Dye BA, Tan S, Smith V, Lewis BG, Barker LK, Thornton-Evans G, *et al.* (2007). Trends in oral health status: United States, 1988-1994 and 1999-2004. *Vital Health Stat 11* 248:1-92.
- Ebersole JL, Cappelli D (2000). Acute-phase reactants in infections and inflammatory diseases. *Periodontol* 2000 23:19-49.
- Eke PI, Thornton-Evans GO, Wei L, Borgnakke WS, Dye BA (2010). Accuracy of NHANES periodontal examination protocols. *J Dent Res* 89:1208-1213.
- Fisher MA, Taylor GW, Shelton BJ, Jamerson KA, Rahman M, Ojo AO, *et al.* (2008). Periodontal disease and other nontraditional risk factors for CKD. *Am J Kidney Dis* 51:45-52.
- Fisher MA, Taylor GW, West BT, McCarthy ET (2011). Bidirectional relationship between chronic kidney and periodontal disease: a study using structural equation modeling. *Kidney Int* 79:347-355.
- Friedewald VE, Kornman KS, Beck JD, Genco R, Goldfine A, Libby P, *et al.* (2009). The American Journal of Cardiology and Journal of Periodontology Editors' Consensus: periodontitis and atherosclerotic cardiovascular disease. *Am J Cardiol* 104:59-68.
- Girndt M, Sester U, Kaul H, Kohler H (1998). Production of proinflammatory and regulatory monokines in hemodialysis patients shown at a single-cell level. *J Am Soc Nephrol* 9:1689-1696.
- Herbelin A, Urena P, Nguyen AT, Zingraff J, Descamps-Latscha B (1991). Elevated circulating levels of interleukin-6 in patients with chronic renal failure. *Kidney Int* 39:954-960.
- Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM (2002). The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int* 62:1524-1538.
- Ioannidou E, Swede H (2011). Disparities in periodontitis prevalence among chronic kidney disease patients. *J Dent Res* 90:730-734.
- Ioannidou E, Kao D, Chang N, Burleson J, Dongari-Bagtzoglou A (2006). Elevated serum interleukin-6 (IL-6) in solid-organ transplant recipients is positively associated with tissue destruction and IL-6 gene expression in the periodontium. *J Periodontol* 77:1871-1878.
- Kshirsagar AV, Moss KL, Elter JR, Beck JD, Offenbacher S, Falk RJ (2005). Periodontal disease is associated with renal insufficiency in the Atherosclerosis Risk In Communities (ARIC) study. *Am J Kidney Dis* 45:650-657.
- Kshirsagar AV, Bombardieri AS, Bang H, Gerber LM, Vupputuri S, Shoham DA, *et al.* (2008). Association of C-reactive protein and microalbuminuria (from the National Health and Nutrition Examination Surveys, 1999 to 2004). *Am J Cardiol* 101:401-406.
- Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, *et al.* (2011). The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 80:17-28.
- Lindhe J, Ranney R, Lamster I, Charles A, Chung CP, Flemmig T, *et al.* (1999). Consensus report: chronic periodontitis. *Ann Periodontol* 4:38.
- Mohadjer L, Montaquila JM, Waksberg J, Bell B, James P, Flores-Cervantes I, *et al.* (1996). National Health and Nutrition Examination Survey III: weighting and estimation methodology. Rockville, MD: Westat, Inc.
- Page RC, Eke PI (2007). Case definitions for use in population-based surveillance of periodontitis. *J Periodontol* 78(7 Suppl):1387S-1399S.
- Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, *et al.* (2003). Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation* 107:499-511.
- Sarnak MJ (2003). Cardiovascular complications in chronic kidney disease. *Am J Kidney Dis* 41(5 Suppl):11S-17S.
- Schwedler S, Schinzel R, Vaith P, Wanner C (2001). Inflammation and advanced glycation end products in uremia: simple coexistence, potentiation or causal relationship? *Kidney Int Suppl* 78:32-36.
- Slade GD, Offenbacher S, Beck JD, Heiss G, Pankow JS (2000). Acute-phase inflammatory response to periodontal disease in the US population. *J Dent Res* 79:49-57.
- Stenvinkel P (2001). Malnutrition and chronic inflammation as risk factors for cardiovascular disease in chronic renal failure. *Blood Purif* 19:143-151.
- Stenvinkel P, Chung SH, Heimbürger O, Lindholm B (2001). Malnutrition, inflammation, and atherosclerosis in peritoneal dialysis patients. *Perit Dial Int* 21(Suppl 3):157-162.
- Stevens LA, Coresh J, Schmid CH, Feldman HI, Froissart M, Kusek J, *et al.* (2008). Estimating GFR using serum cystatin C alone and in combination with serum creatinine: a pooled analysis of 3,418 individuals with CKD. *Am J Kidney Dis* 51:395-406.
- Upadhyay A, Larson MG, Guo CY, Vasani RS, Lipinska I, O'Donnell CJ, *et al.* (2011). Inflammation, kidney function and albuminuria in the Framingham Offspring cohort. *Nephrol Dial Transplant* 26:920-926.