Effect of Periodontitis on Overt Nephropathy and End-Stage Renal Disease in Type 2 Diabetes

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OBJECTIVE — The purpose of this study was to investigate the effect of periodontitis on development of overt nephropathy, defined as macroalbuminuria, and end-stage renal disease (ESRD) in type 2 diabetes.

RESEARCH DESIGN AND METHODS — Individuals residing in the Gila River Indian Community aged ≥25 years with type 2 diabetes, one or more periodontal examination, estimated glomerular filtration rate ≥60 ml/min per 1.73 m^2, and no macroalbuminuria (urinary albumin-to-creatinine ratio ≥300 mg/g) were identified. Periodontitis was classified as none/mild, moderate, severe, or edentulous using number of teeth and alveolar bone score. Subjects were followed to development of macroalbuminuria or ESRD, defined as onset of renal replacement therapy or death attributed to diabetic nephropathy.

RESULTS — Of the 529 individuals, 107 (20%) had none/mild periodontitis, 200 (38%) had moderate periodontitis, 117 (22%) had severe periodontitis, and 105 (20%) were edentulous at baseline. During follow-up of up to 22 years, 193 individuals developed macroalbuminuria and 68 developed ESRD. Age- and sex-adjusted incidence of macroalbuminuria and ESRD increased with severity of periodontitis. After adjustment for age, sex, diabetes duration, BMI, and smoking in a proportional hazards model, the incidences of macroalbuminuria were 2.0, 2.1, and 2.6 times as high in individuals with moderate or severe periodontitis or those who were edentulous, respectively, compared with those with none/mild periodontitis ($P = 0.01$). Incidences of ESRD in individuals with moderate or severe periodontitis or in those who were edentulous were 2.3, 3.5, and 4.9 times as high, respectively, compared with those with none/mild periodontitis ($P = 0.02$).

CONCLUSIONS — Periodontitis predicts development of overt nephropathy and ESRD in individuals with type 2 diabetes. Whether treatment of periodontitis will reduce the risk of diabetic kidney disease remains to be determined.

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Periodontitis is a common infection of the periodontal tissues (1) and a major cause of tooth loss in adults (2,3). The most prevalent form is chronic periodontitis (1). Individuals with diabetes are at increased risk of developing periodontitis, and, once established, periodontitis is more severe in people with diabetes (3–6). Poor glycemic control hastens the progression of periodontitis and, in turn, periodontitis appears to further impair glycemic control (6–8).

Periodontitis predicts cardiovascular disease risk (9) and deaths from diabetic kidney disease and cardiovascular disease in individuals with type 2 diabetes (10). However, the relationship between periodontitis and diabetic kidney disease has not been fully explored. Among nonobese individuals with type 2 diabetes in Japan, IgG titers for *Porphyromonas gingivalis* (a periodontal pathogen) were correlated with the urinary albumin-to-creatinine ratio (ACR), although analyses were not adjusted for confounding factors (11). In the Atherosclerosis Risk in Communities (ARIC) Study, a largely nondiabetic population, periodontitis was associated with a low estimated glomerular filtration rate (GFR) (<60 ml/min per 1.73 m^2), and this finding remained after adjustment for the presence of diabetes and other potential confounding variables (12).

In the present study, we examined the effect of periodontitis on the development of overt nephropathy, defined by macroalbuminuria (ACR ≥300 mg/g), and end-stage renal disease (ESRD) in type 2 diabetes in an American-Indian population.

RESEARCH DESIGN AND METHODS

— Data were collected as part of a longitudinal study of diabetes and its complications in the Gila River Indian Community of Arizona (4). The diabetes study was initiated in 1965, and members of the community are invited to attend a research clinic for examination and screening every 2 years. Ethical approval was obtained from the institutional review boards of the National Institute of Diabetes and Digestive and Kidney Diseases and from the Gila River Indian Community Council.

This analysis includes data from all individuals with diabetes whose heritage was at least half Pima or Tohono O'odham and who had one or more periodontal examinations after 25 years of age at which baseline ACR was <300 mg/g and baseline estimated GFR was ≥60 ml/min per 1.73 m^2. Diabetes was diagnosed according to World Health Organization criteria (13) by a 2-h postload plasma glucose concentration ≥200 mg/dl or from clinical records. Urinary albumin was measured by nephelometric immunoassay (14). Urinary and serum creatinine were

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Abbreviations: ACR, albumin-to-creatinine ratio; ARIC, Atherosclerosis Risk in Communities; ESRD, end-stage renal disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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measured by a modification of the Jaffe reaction (15). Serum creatinine values were calibrated to the Modification of Diet in Renal Disease (MDRD) Study laboratory, and these values were used to estimate GFR with the four-variable MDRD equation, categorizing individuals as of nonblack ethnicity (16). The correlation between MDRD-estimated GFR and iothalamate GFR in this American-Indian population from preliminary validation work is 0.80 ($n = 201$) (17). The cutoff of 60 ml/min per 1.73 m^2 GFR was chosen on the basis of the guidelines of the National Kidney Foundation to exclude individuals with preexisting impaired GFR (16). ESRD was defined as the requirement for renal replacement therapy due to diabetes or death from diabetic nephropathy. Data on ESRD were collected independently of the biennial research examinations and were complete to 31 December 2002.

Periodontal examinations were conducted between 1983 and 1990. Panoramic radiographs were evaluated and scored by a single examiner (M.S.). Alveolar bone loss was determined by scoring percent bone loss from the cementoenamel junction to the apex at the deepest point on the mesial or distal surfaces of each tooth present, excluding third molars. Periodontitis was classified in order of severity by the number of missing teeth and percent alveolar bone loss as *1*) none/mild periodontitis, defined as ≥24 teeth, of which <6 had 25–49% bone loss and none had ≥50% bone loss; *2*) moderate periodontitis, defined as ≥15 teeth, of which <7 had 50–74% bone loss and <4 had ≥75% bone loss; *3*) severe periodontitis, defined as 1–14 teeth or greater bone loss than in previous categories; and *4*) edentulous. In previous reports, 72% of the tooth loss in this population is attributable to periodontitis (3), and, as such, missing teeth were considered to be lost due to periodontitis, and edentulous individuals were considered to have the most severe manifestation of periodontitis. Although our definition of periodontitis does not permit us to differentiate between aggressive and chronic periodontitis, the majority of cases are likely to represent chronic periodontitis (1).

HbA1 was measured by agar gel electrophoresis until 1989, after which A1C was measured by high-performance liquid chromatography. A1C values were estimated from HbA1 values using the equation A1C = (0.99 × HbA1) – 1.535 (18). BMI was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined by a BMI ≥30 kg/m^2. Smoking status was self-reported as nonsmoking (<100 cigarettes in a lifetime), prior smoking (have not smoked for past year), currently smoking ≤1 pack/day, and currently smoking >1 pack/day. Only five individuals reported currently smoking >1 pack/day, and smoking was considered as current smoking "yes" or "no" for analysis. Blood pressure was measured at the first and fourth Korotkoff sounds with the subject in the supine position. Mean arterial pressure was calculated as two-thirds diastolic blood pressure + one-third systolic blood pressure. Hypertension was defined by diastolic blood pressure ≥80 mmHg, systolic blood pressure ≥130 mmHg, or current usage of antihypertensive medicine (19).

Statistical analysis

Characteristics of the individuals across categories of periodontitis were explored using the nonparametric Kruskal-Wallis test for continuous variables and the Mantel extension test for categorical variables. Incidence rates were computed as the number of new occurrences of macroalbuminuria or ESRD per 1,000 person-years at risk by age and sex and by periodontitis status, standardized to the 1980 community population. If subjects changed periodontitis strata during follow-up, their person-time was apportioned to the appropriate stratum. Follow-up accumulated only while individuals resided within the community and extended from the date of the first diabetes research examination after the age of 25 years that included a periodontal examination to development of macroalbuminuria or ESRD. For individuals who did not develop either outcome, follow-up time was censored: in the case of the macroalbuminuria analysis at the date of the last research examination and for the ESRD analysis at development of ESRD not due to diabetes, date of death from causes other than diabetic nephropathy if death occurred before 31 December 2002 or at 31 December 2002. Linear association was computed by the Mantel extension test, modified for person-time denominators.

The effect of periodontitis on incidence of macroalbuminuria and ESRD was also examined using time-dependent Cox proportional hazards models to control for the effects of potentially confounding variables. Final models were adjusted for age at baseline, sex, duration of diabetes at baseline, BMI, and current smoking. A1C was considered both a potential confounder and intermediary in the relationship of periodontitis to macroalbuminuria and ESRD, and final models were repeated with additional adjustment for A1C. Assumptions of proportionality were checked using log follow-up time interaction terms for each baseline variable. Residual versus linear predictor plots were checked for outliers. Product terms of predictor variables, including sex interactions, did not improve the models and were not included. To maintain proportionality assumptions, final models for macroalbuminuria were stratified by baseline age and BMI, and final models for ESRD were stratified by baseline BMI and current smoking. Such stratification controls for confounding by the variables but does not allow estimation of their effects. Time-dependent models were constructed to allow the values for periodontitis, A1C, and current smoking (macroalbuminuria only) to change with time. The overall effect of periodontitis on the incidence of macroalbuminuria and ESRD was assessed by likelihood ratio tests comparing time-dependent models with and without terms for periodontitis. Statistical analyses were performed using SAS software version 8 (SAS Institute, Cary, NC).

RESULTS — Among the 529 individuals (168 men and 361 women) included in this study, 107 (20%) had none/mild peritonitis, 200 (38%) had moderate peritonitis, and 117 (22%) had severe periodontitis, and 105 individuals (20%) were edentulous at baseline (Table 1). Age, diabetes duration, A1C (all $P < 0.0001$), and hypertension ($P = 0.01$) at baseline were positively associated with severity of periodontitis, whereas BMI and obesity were negatively associated with severity of periodontitis (both $P < 0.0001$). During a median follow-up of 9.4 years (range 0.03–21.6 years), 193 individuals developed macroalbuminuria, and during a median follow-up of 14.9 years (0.03–21.8 years), 68 individuals developed ESRD. The unadjusted incidence of macroalbuminuria and ESRD were 37.5 cases/1,000 person-years and 9.0 cases/1,000 person-years, respectively. Incidence rates of macroalbuminuria and ESRD by age and sex are shown in Table 2.

Age- and sex-adjusted incidence rates of macroalbuminuria and ESRD were

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Table 1—*Characteristics of the individuals in this analysis by periodontitis status at baseline*

Continuous variables	Periodontitis status				*P* for trend
	None or mild	Moderate	Severe	Edentulous	
n	107	200	117	105	
Age (years)	33 (25–72)	44 (25–72)	49 (26–77)	55 (25–79)	<0.0001
Diabetes duration (years)	1.9 (0.0–19.7)	4.3 (0.0–26.4)	7.9 (0.0–24.6)	12.3 (0.0–32.4)	<0.0001
A1C (%)	6.1 (3.8–13.0)	7.4 (2.7–13.4)	9.4 (2.8–15.9)	9.1 (4.2–14.2)	<0.0001
BMI (kg/m^2)	38.6 (24.6–71.1)	33.3 (21.0–55.0)	30.2 (20.5–54.4)	29.8 (21.9–65.4)	<0.0001
MAP (mmHg)	88 (67–117)	91 (57–133)	92 (69–135)	92 (63–128)	0.25
Categorical variables					
Male	24 (22.4)	80 (40.0)	39 (33.3)	25 (23.8)	0.66
Obese	93 (86.9)	141 (70.5)	61 (52.1)	51 (48.6)	<0.0001
Hypertensive	47 (43.9)	98 (49.8)	64 (55.7)	63 (60.0)	0.01
Currently smoking	21 (19.6)	53 (26.5)	26 (22.2)	14 (13.5)	0.15

Data are median (range) or *n* (%). Total $n = 529$. Missing data: $n = 3$ for baseline mean arterial pressure (MAP), $n = 13$ for baseline A1C, $n = 5$ for baseline hypertension, and $n = 1$ for baseline smoking.

positively associated with severity of periodontitis ($P = 0.0001$ and $P = 0.003$, respectively; Fig. 1). Moderate and severe periodontitis and edentulousness predicted the development of macroalbuminuria in a dose-dependent manner after adjustment for age, sex, duration of diabetes, and BMI at baseline and updated periodontal and smoking status at each examination (Table 3). The hazard rate ratios (HRRs) for moderate or severe periodontitis and edentulousness were 2.0 (95% CI 1.2–3.5), 2.1 (1.2–3.8), and 2.6 (1.4–4.6), respectively (overall $P = 0.01$). This relationship was attenuated after adjustment for A1C, updated at each examination; HRR for moderate periodontitis was 1.7 (0.95–3.0), for severe periodontitis was 1.6 (0.9–3.0), and for edentulousness was 2.0 (1.1–3.6) (overall $P = 0.17$). Periodontitis also predicted the development of ESRD after adjustment for age, sex, duration of diabetes, BMI, and smoking status at baseline and updated periodontal status at each examination (overall $P = 0.02$) (Table 3). The relationship between periodontitis and ESRD was also attenuated after adjustment for A1C, updated at each examination; HRR for moderate periodontitis was 1.3 (0.4–4.9), for severe periodontitis was 1.8 (0.5–6.7), and for edentulousness was 2.5 (0.7–9.4) (overall $P = 0.21$).

CONCLUSIONS — Periodontitis predicts the development of overt nephropathy and ESRD in a dose-dependent manner in individuals with little or no preexisting kidney disease after adjustment for age, sex, duration of diabetes, BMI, and current smoking. These findings confirm the emerging evidence of an independent association between periodontitis and the development of diabetic kidney disease. To our knowledge, only two studies have investigated the effect of periodontitis on early kidney disease (11,12). These studies were cross-sectional; one was in a largely nondiabetic population (12), and the other did not explore the effect of potential confounders (11). The present study, however, was prospective, conducted exclusively in individuals with diabetes, and included a proportionately large number of individuals with kidney disease. Data on change in periodontal status were collected (on up to four occasions for each individual), and models allowed periodontitis and A1C to change at each examination. Current smoking data were also updated at each examination in the macroalbuminuria analysis. Furthermore, all of the study participants had an estimated GFR ≥60 ml/min per 1.73 m^2 and did not have macroalbuminuria at baseline. Macroalbuminuria and not microalbuminuria was chosen as an outcome in our analysis because microalbuminuria is much more likely to regress than macroalbuminuria, and restricting our dataset to individuals without microalbuminuria at baseline reduced our sample size by approximately one-third.

Implicit in a time-dependent analysis

Table 2—*Incidence of overt nephropathy, characterized by macroalbuminuria (MA), and ESRD per 1,000 person-years (PYRs) by age and sex in an American-Indian population with type 2 diabetes*

Age-group (years)	Men			Women		
	Cases	PYRs	Incidence	Cases	PYRs	Incidence
MA						
25–44	14	542	25.8	34	1,386	24.5
45–64	37	792	46.7	77	1,864	41.3
≥65	6	128	46.8	25	436	57.4
ESRD						
25–44	3	658	4.6	3	1,660	1.8
45–64	15	1,265	11.9	26	2,592	10.0
≥65	3	320	9.4	18	1,033	17.4

$n = 529$.

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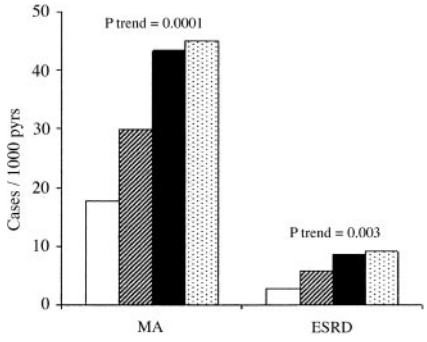

Figure 1— *Age- and sex-adjusted incidence of overt nephropathy, characterized by macroalbuminuria (MA), and ESRD per 1,000 person-years across categories of periodontitis in an American-Indian population with diabetes (n = 529).* □*, none/mild periodontitis;* ▨*, moderate periodontitis;* ■*, severe periodontitis;* ▩*, edentulous.*

are the assumptions that the study exposure (in this case, periodontitis) does not affect any covariates used as regressors and that there is no confounding within levels of the other covariates. These assumptions may not be valid when the exposure and the covariates vary over time, because a covariate may be affected by the exposure and also be a confounder. In the present analysis, the level of hyperglycemia may be a confounder because it is a known risk factor for kidney disease (20) and is associated with periodontitis (3,4,6). On the other hand, the level of glycemia also rises as a consequence of periodontitis (6,7). A1C may therefore be both a confounder and an intermediate variable on the causal pathway between periodontitis and kidney disease, and a proportional hazards analysis that includes A1C as a time-dependent covariate will underestimate the effect of periodontitis on the development of kidney disease. Nevertheless, exclusion of this variable may cause confounding. Accordingly, we examined the effect of periodontitis on kidney disease by using two models, but we favor the model that did not control for A1C (Table 3) because this variable is almost certainly an intermediate variable in the pathway of interest.

BMI was inversely associated with severity of periodontitis at baseline in this analysis (Table 1), in contrast to the positive association between BMI and periodontitis reported in the ARIC Study 12). However, the ARIC Study was conducted in a predominantly nondiabetic population. After diabetes diagnosis, BMI declines in Pima Indians, and this decline continues with increasing diabetes duration (21). Given that poor glycemic control hastens the progression of periodontitis (6,8) and glycemic control tends to worsen with increasing diabetes duration (22), an inverse association between BMI and severity of periodontitis in individuals with diabetes is expected. Indeed, after adjustment for age, diabetes duration, and A1C, the association between BMI and periodontitis at baseline was no longer significant (data not shown).

Smoking is associated with both periodontitis (23,24) and kidney disease (25,26) and may confound the relationship between these diseases. Nevertheless, fewer than 1% of adult Pima Indians smoke one pack or more of cigarettes per day. In this population, current smoking is not a prominent risk factor for fatal coronary heart disease (27) and did not explain the relationship between periodontitis and kidney disease in the present study. However, given our measures of smoking, the possibility of residual confounding due to smoking in this analysis cannot be excluded. High blood pressure is strongly associated with diabetic kidney disease (28); however, hypertension was not considered a potential confounding factor in our analysis, because when we adjusted our final time-dependent models for hypertension, the association of periodontitis with macroalbuminuria and ESRD remained unchanged (data not shown). Furthermore, to our knowledge there is no published evidence linking blood pressure with risk of development of periodontitis. The positive association between the presence of hypertension and severity of periodontitis at baseline in the present analysis was attributable, in part, to the higher average age of individuals who were edentulous or had severe periodontitis (data not shown). Finally, the effect of periodontitis on macroalbuminuria and ESRD may be underestimated to the extent that complete tooth loss was due to factors other than periodontitis.

A proposed mechanism for the effect of periodontitis on the development of kidney disease is systemic inflammation. Both periodontitis and kidney disease are associated with inflammatory markers such as C-reactive protein (29,30), and chronic low-level inflammation associated with periodontitis may lead to endothelial dysfunction, which plays a role in the pathogenesis of kidney disease (31,32). Periodontitis is treatable, and treatment by tooth extraction (33) or other mechanical procedures and locally administered antibiotics (34) lowers levels of C-reactive protein and other inflammatory markers. In edentulous individuals, the potentially deleterious effects of sys-

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Table 3—*Time-dependent Cox proportional hazards models of the effect of periodontitis (PD) on the incidence of overt nephropathy, characterized by macroalbuminuria (MA), and ESRD in an American-Indian population with type 2 diabetes*

	Effect of PD on MA*		Effect of PD on ESRD†	
Variable	HRR (95% CI)	*P* value	HRR (95% CI)	*P* value
Moderate PD (vs. none/mild PD)	2.0 (1.2–3.5)	0.01‡	2.3 (0.6–8.1)	0.02‡
Severe PD (vs. none/mild PD)	2.1 (1.2–3.8)		3.5 (0.96–12.4)	
Edentulous (vs. none/mild PD)	2.6 (1.4–4.6)		4.9 (1.4–17.4)	
Age at baseline (10 years)	—	—	0.8 (0.6–1.0)	0.05
Sex (male/female)	0.8 (0.6–1.2)	0.30	0.8 (0.4–1.4)	0.37
Diabetes duration at baseline (10 years)	2.1 (1.6–2.7)	<0.0001	2.4 (1.5–3.6)	0.0001
Smoking (no/yes)	1.2 (0.8–1.7)	0.47	—	—

n = 515. *Model stratified by baseline age and BMI because these variables violated the proportionality assumption. †Model stratified by baseline BMI and smoking because these variables violated the proportionality assumption. ‡*P* value for overall effect of PD on outcome obtained by likelihood ratio test comparing models with and without terms for PD.

temic inflammation on kidney function could occur during the period of active periodontal infection and accumulate during the lifetime of the individual. This hypothesis is supported by the observation that the strongest predictive effect of periodontal status on kidney disease was found in edentulous individuals (Table 3). Cardiovascular disease prevalence and risk is higher or equivalent in edentulous individuals compared with that in individuals with severe periodontitis in some (35,36) but not all studies (37).

In summary, periodontitis predicts the development of both overt nephropathy and ESRD in an American-Indian population with type 2 diabetes. Future studies investigating measures of inflammatory markers may help elucidate the potential mechanisms for the association between periodontitis and diabetic kidney disease. Whether successful management of periodontitis will reduce the risk of diabetic kidney disease, however, remains to be determined.

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