Periodontal Disease and Mortality in Type 2 Diabetes

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OBJECTIVE — Periodontal disease may contribute to the increased mortality associated with diabetes.

RESEARCH DESIGN AND METHODS — In a prospective longitudinal study of 628 subjects aged ≥35 years, we examined the effect of periodontal disease on overall and cardiovascular disease mortality in Pima Indians with type 2 diabetes. Periodontal abnormality was classified as no or mild, moderate, and severe, based on panoramic radiographs and clinical dental examinations.

RESULTS — During a median follow-up of 11 years (range 0.3–16), 204 subjects died. The age- and sex-adjusted death rates for all natural causes expressed as the number of deaths per 1,000 person-years of follow-up were 3.7 (95% CI 0.7–6.6) for no or mild periodontal disease, 19.6 (10.7–28.5) for moderate periodontal disease, and 28.4 (22.3–34.6) for severe periodontal disease. Periodontal disease predicted deaths from ischemic heart disease (IHD) (P trend = 0.04) and diabetic nephropathy (P trend < 0.01). Death rates from other causes were not associated with periodontal disease. After adjustment for age, sex, duration of diabetes, HbA_{1c}, macroalbuminuria, BMI, serum cholesterol concentration, hypertension, electrocardiographic abnormalities, and current smoking in a proportional hazards model, subjects with severe periodontal disease had 3.2 times the risk (95% CI 1.1–9.3) of cardiorenal mortality (IHD and diabetic nephropathy combined) compared with the reference group (no or mild periodontal disease and moderate periodontal disease combined).

CONCLUSIONS — Periodontal disease is a strong predictor of mortality from IHD and diabetic nephropathy in Pima Indians with type 2 diabetes. The effect of periodontal disease is in addition to the effects of traditional risk factors for these diseases.

Diabetes Care **28:27–32, 2005**

Periodontal disease, a common chronic oral inflammatory disease, is characterized by destruction of soft tissue and bone. Modulation of host factors, such as diabetes, is important for the progression or worsening of periodontal disease (1,2). Although the pathogenesis of periodontal disease in diabetes remains unclear, most evidence suggests that it may result from prolonged exposure to hyperglycemia and occurs with the greatest frequency and severity in those with poor glycemic control (3–5). Several epidemiological studies suggest that periodontal infection may be a risk factor for heart disease (reviewed in 6). Diabetic persons with severe periodontal disease may be particularly susceptible to microvascular and macrovascular complications, which are primarily responsible for the increased morbidity and mortality associated with diabetes. To our knowledge, no previous studies have investigated the risk of cardiovascular disease (CVD) mortality associated with periodontal disease in patients with diabetes.

The aim of this study was to examine the effect of periodontal disease on overall and CVD mortality in Pima Indians with type 2 diabetes, after accounting for the impact of common risk factors for both diseases.

RESEARCH DESIGN AND METHODS

Population study and medical examination

Residents of the Gila River Indian Community of Arizona, most of whom are Pima or closely related Tohono O'odham Indians, participate in a longitudinal population-based study of diabetes and its complications conducted by the National Institute of Diabetes and Digestive and Kidney Diseases (7). Approximately every 2 years, each member of the community aged ≥5 years is invited to participate in a standardized examination (biennial examination) that includes a medical history, physical examination, and measurement of BMI, blood pressure, plasma glucose level, HbA_{1c} level, serum cholesterol concentration, and albuminuria. HbA_{1c} was measured until 31 December 1989 by agar gel electrophoresis (8), after which HbA_{1c} was measured by high-performance liquid chromotomography (9).

Among 133 subjects (not from this study) in whom both variables were measured, the correlation between the two measures was 0.92. The linear regression formula from this comparison (HbA_{1c} = 0.99 × HbA_{1c} − 1.535) was used to estimate HbA_{1c} in subjects in this study in whom HbA_{1c} was measured (10). Subjects were considered hypertensive if their

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Received for publication 4 June 2004 and accepted in revised form 19 September 2004.
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Abbreviations: CVD, cardiovascular disease; ECG, electrocardiogram; IHD, ischemic heart disease; PAF, population attributable fraction.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

systolic blood pressure was ≥140 mmHg, their diastolic blood pressure was ≥90 mmHg, or they were taking antihypertensive drugs. Smoking was assessed by an interviewer-administered questionnaire. Current smoking was defined as cigarette smoking in any amount during the past year. Previous smokers who reported no smoking during the past year were included in the nonsmoking category. Twelve-lead electrocardiograms (ECGs) were recorded in all subjects during the first biennial examination and during each examination subsequent to the 15th birthday. All ECGs were interpreted and classified according to the Minnesota Code by the same cardiologist, who had no knowledge of the clinical data. Major ECG abnormalities were identified according to the Tecumseh criteria (11,12). Total serum cholesterol was measured by a colorimetric method (13). A urinary albumin-to-creatinine ratio (mg albumin/g creatinine) was used as an estimate of albumin excretion rate (14). Macroalbuminuria was defined as an albumin-to-creatinine ratio ≥300 mg/g. Diabetes was defined by 1985 World Health Organization criteria (15) if plasma glucose concentration was ≥200 mg/dl 2 h after a 75-g oral glucose load or if a clinical diagnosis was documented in the medical record.

Dental examination

Periodic dental examinations were conducted from January 1983 to September 1990 as part of the biennial research visits. Dentists performed the examinations without knowledge of the patient's medical status. Each examination included an evaluation of the oral mucous membranes by visual and digital examination of six index teeth or their substitutes (16) and an evaluation of alveolar bone loss score from a panoramic radiograph of all existing teeth (OP-5; Siemens, Munich, Germany). Probing attachment levels were measured at four sites: midbuccal, midlingual, mesial interproximal point, and distal interproximal point. The median probing attachment loss at 24 sites (four sites on each of six index teeth) and median alveolar bone loss scores among all teeth were used as two measures of the presence and severity of periodontal disease. For these analyses, a missing tooth was assigned a value higher than the maximum recorded measurements so that edentulous patients or patients with missing index teeth could be included. A total of 72% of the extractions in this population were due to periodontal disease (1). Periodontal disease was classified as no or mild, moderate, and severe. Individuals with no or mild periodontal disease had 15 or more teeth, a median bone loss score <50%, and median attachment loss of <1 mm. Individuals with moderate periodontal disease had 15 or more teeth, a median bone loss score of 50–75%, or a median attachment loss of 2–5 mm. Those with severe periodontal disease had less than 15 teeth or a median bone loss score of >75% or a median attachment loss of ≥6 mm. A more detailed description of the dental examination is provided elsewhere (1).

Of a total of 772 diabetic individuals aged ≥35 years who lived in Gila River Indian community at any time between 1 January 1983 and 30 September 1990, whose heritage was at least 50% Pima or Tohono O'odham, 144 subjects (19%) were excluded from a particular examination for various reasons, including patient refusal (no radiograph and/or probing), pregnancy (no radiograph), heart conditions requiring antibiotic prophylaxis (no probing), mixed dentition (no bone loss score), equipment failure (no radiograph), inability to position patient (no radiograph), or no clinical examination (no probing).

The study population consisted of 628 diabetic individuals who had undergone at least one dental examination with both radiographic bone scores and clinical assessment of attachment levels.

Assessment of vital status

Vital status of all subjects was ascertained as of December 1998. For all deaths, the underlying and contributing causes were assessed by review of clinical reports and reports of autopsy, medical examiner findings, and death certificates (17). The adjudicated causes were coded using terminology and codes of the ICD-9 in accordance with the guidelines of the National Center for Health Statistics. Deaths were considered "natural" if they were due to disease (ICD-9 codes 001.0–799.9) and "external" if they were due to injury or poisoning (ICD-9 codes E800.0-E999.9). The codes for other causes are given in Table 1. Death rates due to ischemic heart disease (IHD) and diabetic nephropathy were analyzed together as a category of cardiorenal disease.

Statistical analysis

Death rates were calculated as the number of deaths per 1,000 person-years of follow-up after the age of 35 years. The period of risk extended from the initial dental examination to death or December 1998. When subjects were reexamined and the periodontal classification changed, the new values were used for subsequent follow-up. Death rates were age- and sex-adjusted to the 1985 Pima Indian population.

The effect of periodontal disease on mortality was examined using a time-dependent Cox proportional hazards model to control for the effect of potentially confounding variables. If the values of variables changed at reexamination, the new values were included for the subsequent times. For this analysis, severe periodontal disease was compared with the reference group of no or mild and moderate periodontal disease combined. To allow for the nonlinear effects of BMI on mortality (18), a quadratic term was used to adjust for BMI in the Cox proportional hazards models. To assess the possibility of effect modification, pairwise interaction terms between periodontal disease and sex, age, duration of diabetes, and smoking were evaluated.

The age- and sex-adjusted population attributable fraction (PAF) was calculated by the weighted-sum method (19).

$$\mathrm{PAF} = \Sigma\, w_j\, \mathrm{PAF}_j$$

where PAF_j represents population attributable risk for the jth stratum of age and sex and w_j represents the number of deaths observed in the jth stratum divided by the total number of deaths. This method of calculating attributable fraction controls for confounding by age and sex.

RESULTS — Clinical and demographic features of the study population at the baseline examination are shown in Table 2. Nearly 60% of the population (373) had severe periodontal disease, and 70% (263) of those with severe periodontal disease were edentulous. In general, individuals with severe periodontal disease were older and had longer duration of diabetes, higher fasting glucose level, HbA_{1c} level, total cholesterol concentration, and higher prevalence of macroalbuminuria, hypertension, and ECG abnormalities. Individuals with severe

Table 1—*Number of deaths and death rates in diabetic Pima Indians by periodontal disease*

	Periodontal disease						
	No or mild (1,161 Pyrs)		Moderate (1,365 Pyrs)		Severe (4,040 Pyrs)		
Underlying cause of death (ICD-9 codes)	*n*	DR	*n*	DR	*n*	DR	*P* trend
All natural causes	6	3.7	23	19.6	155	28.4	<0.01
IHD (410.0–414.9)	0	0	6	4.8	38	5.7	0.04
Diabetic nephropathy (250.4)	0	0	1	0.5	27	5.3	<0.01
Cardiorenal (IHD + diabetic nephropathy)	0	0	7	5.3	65	11.0	<0.01
Other CVD (390.0–459.9)*	1	0.5	2	1.1	7	1.4	0.89
Other diabetes-related conditions (250.0–250.9)†	1	0.8	0	0	6	1.0	0.65
Infections‡	2	1.2	2	2.7	22	4.4	0.20
Malignancy (140.0–208.9)	1	0.6	3	3.2	21	4.3	0.37
Gastrointestinal diseases (520.0–579.9)	1	0.6	6	5.0	19	4.0	0.37
Other natural causes	0	0	3	2.5	15	2.5	0.37
All external causes	1	0.7	6	4.3	13	3.4	0.44

*Excluding IHD; †excluding diabetic nephropathy; ‡ICD-9 codes for infections: 001.0–139.8; 320.0–326.9; 460.0–466.1; 480.0–487.8; 590.9–599.0; 680.0–686.9; 729.4. DR, death rate per 1,000 person-years (Pyrs).

periodontal disease had lower BMI and lower smoking rates than those with no or mild or moderate periodontal disease.

During follow-up, which averaged 11 years (range 0.3–16), 204 of the 628 study subjects died (Table 2). Most CVD deaths (44 of 54) were attributed to IHD, and most of the diabetes-related deaths (28 of 35) were attributed to diabetic nephropathy. Other CVD deaths and other diabetes-related deaths were not significantly associated with periodontal disease. IHD and diabetic nephropathy deaths combined (cardiorenal, $n = 72$) were the leading underlying cause of death in both sexes (death rate: 8.8/1,000 person-years in men, 8.0/1,000 person-years in women). The age-sex–adjusted death rate per 1,000 person-years for IHD was 0 among subjects with no or mild periodontal disease, 4.8 (95% CI 0.5–9.1) among those with moderate periodontal disease, and 5.7 (3.6–7.7) among people with severe periodontal disease (P trend = 0.04). The death rates per 1,000 person-years for diabetic nephropathy ($n = 28$) were 0 among those with no or mild periodontal disease, 0.5 (0.4–1.3) in individuals with moderate periodontal disease, and 5.3 (2.0–8.5) among those with severe periodontal disease (P trend < 0.01).

The age-sex–adjusted death rate for all natural causes of death was also significantly lower in individuals with no or mild periodontal disease (3.7 [0.7–6.6]) compared with moderate periodontal disease (19.6 [10.7–28.5]) and severe periodontal disease (28.4 [22.3–34.6]) (P trend < 0.01). After exclusion of cardiorenal deaths, the rates were 3.7 (0.7–6.6) for no or mild periodontal disease, 14.4 (16.6–22.1) for moderate periodontal disease, and 17.5 (12.7–22.3) for severe periodontal disease (Fig. 1), and the positive trend was weaker ($P = 0.05$).

In subjects with severe periodontal disease, the death rate from IHD was 2.3 (0.9–5.8) times as high and the death rate from diabetic nephropathy was 8.5 (1.1–65.0) times as high as in those with less severe periodontal disease (no or mild and moderate periodontal disease combined), after adjustment for age, sex, and duration of diabetes in a Cox proportional hazards model. Among those who died of IHD, 55% (24 of 44) had advanced diabetic kidney disease; 4 patients had elevated serum creatinine concentrations (≥2.0 mg/dl), and 20 patients were receiving renal replacement therapy. When both renal and CVD (cardiorenal) deaths were analyzed, the death rate from cardiorenal disease in subjects with severe periodontal disease was 3.5 (1.2–10.0) times as high as in those with less severe peri-

Table 2—*Baseline characteristics of 628 diabetic individuals*

	Periodontal disease		
	No or mild	Moderate	Severe
n (men/women)	39/80	56/80	127/246
Age (years)	43 ± 7	47 ± 10	55 ± 11
Fasting glucose (mmol/l)	10.0 ± 4.1	10.9 ± 4.6	11.9 ± 4.4
Duration of diabetes (years)	5.2 ± 5.9	7.4 ± 6.7	12.8 ± 7.4
HbA_{1c} (%)	7.5 ± 2.4	8.1 ± 4.6	8.9 ± 2.5
BMI (kg/m^2)	36 ± 9	35 ± 7	31 ± 9
Cholesterol (mmol/l)	4.7 ± 1.0	4.5 ± 8	4.8 ± 1.1
Smoking			
Never	60	56	65
Past (none in last year)	25	19	17
Up to one pack/day	15	23	17
More than one pack/day	0	2	1
ECG abnormalities	0	4	8
Hypertension	31	39	48
Macroalbuminuria	3	13	31

Data are means ± SD or percent. Numbers of missing values for some variables are as follows: HbA_{1c}, 63; BMI, 2; current smoking, 3; ECG abnormalities, 30.

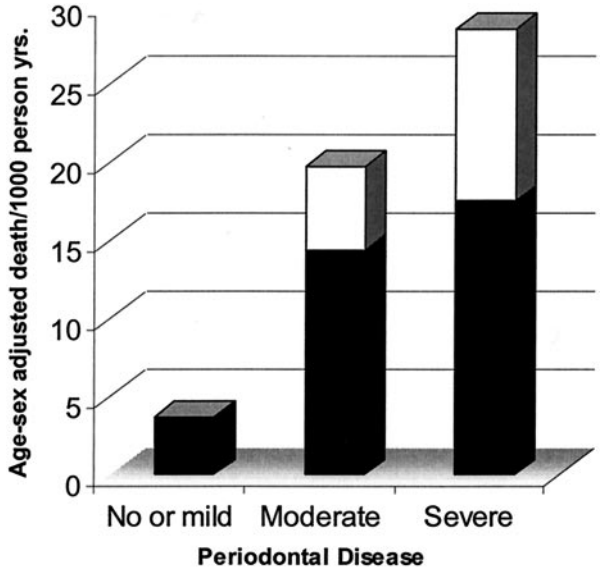

Figure 1—*Mortality rates for all natural causes by periodontal disease (adjusted for age and sex to the 1985 Pima Indian population). □, cardiorenal deaths; ■, all other natural deaths.*

odontal disease after adjustment for age, sex, duration of diabetes, BMI, hypertension, fasting plasma glucose concentration, serum cholesterol concentration, ECG abnormalities, macroalbuminuria, and current smoking behavior (Table 3). The results were similar when HbA_{1c} was substituted for fasting plasma glucose concentration in the proportional hazards model (data not shown).

The interaction term between periodontal disease and age was significant in predicting cardiorenal deaths ($P = 0.01$); therefore, the hazard rate ratios were examined by age-groups. Adjusted for sex, the hazard rate ratio for periodontal disease was 14.8 (3.5–63.2) in the age-group 35–54 years and 3.3 (0.8–14.0) in the age-group ≥55 years. Accordingly, as shown in Table 4, the fraction of cardiorenal deaths attributable to exposure to severe periodontal disease was higher in younger age-groups. The age- and sex-adjusted fraction of cardiorenal deaths attributable to exposure to severe periodontal disease was 57%. Other interaction terms between periodontal disease and sex, duration of diabetes, and smoking were not statistically significant. Such terms, therefore, were not included in the final models.

CONCLUSIONS — Death rates from IHD and nephropathy were higher in diabetic Pima Indians with severe periodontal disease than in those with no or mild periodontal disease or moderate periodontal disease. Death rates from other causes were less affected by the presence of severe periodontal disease. The fact that both IHD and diabetic nephropathy were affected is not surprising, because they share many of the same risk factors. Patients undergoing hemodialysis and others with chronic kidney disease face a greatly increased risk of atherosclerotic complications, including myocardial infarction, cerebrovascular accidents, and sudden death due to cardiac arrhythmia (20). Furthermore, among diabetic Pima Indians, death rates for IHD have increased in recent years, largely as a result of the wide availability of renal replacement therapy and the corresponding reduction in deaths from diabetic nephropathy (21). Therefore, the distinction between IHD and renal disease as a cause of death may be partly artifactual, because they are closely competing causes of death. Accordingly, we combined IHD and diabetic nephropathy deaths into one category of cardiorenal deaths.

Other risk factors for cardiorenal disease, such as older age, longer duration of diabetes, poor glycemic control, higher serum cholesterol concentration, and higher prevalence of macroalbuminuria and hypertension, are also found more frequently in patients with severe periodontal disease and may contribute to the higher death rate from cardiorenal disease. Poor glycemic control, in particular, is a widely recognized risk factor for the macrovascular (CVD) and microvascular (retinopathy, nephropathy, and neuropathy) complications of diabetes, and previous studies have found an association between poor glycemic control and poor periodontal health (3–5). Nevertheless, in the present study, the association between periodontal disease and cardiorenal deaths remained significant after

Table 3—*Estimated effect (death rate ratio and 95% CI) of periodontal disease and other factors on deaths from cardiorenal disease*

Covariates	Death rate ratio (95% CI)	*P* value
Model 1*		
Adjusted for age, sex, and duration of diabetes		
Periodontal disease (severe versus no or mild and moderate)	4.5 (2.0–10.2)	<0.01
Model 2†		
Adjusted for age, sex, and BMI		
Periodontal disease (severe versus no or mild and moderate)	3.5 (1.2–10.0)	0.02
Duration of diabetes (per 5 years)	1.5 (1.2–1.9)	<0.01
Fasting glucose	1.0 (0.9–1.2)	0.63
Current smoking (present versus absent)	1.9 (0.8–4.3)	0.11
Total cholesterol	2.0 (1.5–2.6)	<0.01
Macroalbuminuria (present versus absent)	1.9 (1.1–3.4)	0.03
Hypertension (present versus absent)	1.8 (1.1–3.2)	0.03
ECG abnormalities (present versus absent)	1.9 (0.9–4.1)	0.10

*Model 1: adjusted for age, sex, and duration of diabetes (72 events/628 subjects). †Model 2: analysis of BMI includes a quadratic term (see STATISTICAL ANALYSIS section; due to missing values for some covariates, the numbers dropped to 62 events/579 subjects).

Table 4—*Estimation of weighted-sum population attributable fraction*

Age	Sex	No severe periodontal disease		Severe periodontal disease		MR_0	MR_t	PAF	w_j	w_j* PAF
		Death	Person-years	Death	Person-years					
35–44 years	M	0	279.2	1	133.3	0	0.002	1	0.013	0.023
	F	0	443.2	0	193.7	0	0	—	0	—
45–54 years	M	1	449.6	5	416.8	0.002	0.006	0.678	0.083	0.056
	F	0	629.6	4	662.2	0	0.003	1	0.055	0.055
55–64 years	M	2	179.7	8	396.5	0.011	0.017	0.358	0.138	0.049
	F	2	363.5	13	991.4	0.005	0.011	0.503	0.208	0.104
≥65 years	M	1	74.4	5	309.2	0.013	0.015	0.140	0.083	0.011
	F	1	106.3	29	936.5	0.009	0.028	0.672	0.416	0.280
Sum		7	2,525.4	65	4,039.6	0.002	0.010	0.747	1	0.572

MR_0, mortality rates in unexposed; MR_t, mortality rates in the total population; PAF $(MR_t - MR_0)/MR_t$; w_j, number of deaths/total number of deaths.

adjustment for glycemic control, measured either by fasting glucose concentration or by HbA_{1c}. In addition to these risk factors, diabetic Pima Indians with severe periodontal disease had lower BMI, which may reflect underlying illness because it is associated with higher mortality rates in this population (18).

Heavy smoking is strongly associated with both periodontal disease and CVD (22) and undoubtedly confounds the relationship between these diseases (23–28). In the present study, however, smoking was not associated with periodontal disease. Of the subjects in this study, >60% reported never smoking, and heavy smoking (more than one pack a day) was reported by <1%. As shown in previous studies, the prevalence of heavy smoking is low in Pima Indians (29), and smoking is not a major significant risk factor for coronary heart disease in this population (30). Analyses of smoking using different groupings of current, never, and past smokers gave similar results to those presented here. Smoking did not predict cardiorenal mortality in this study, and severe periodontal disease remained a strong and significant predictor of cardiorenal deaths in both smokers and nonsmokers.

Most individuals with severe periodontal disease were edentulous, and 72% of tooth extractions in this population were due to periodontal disease (1). Misclassification in the severe periodontal disease group could occur, to the extent that edentulous subjects were edentulous for reasons other than periodontal disease. Nevertheless, exclusion of edentulous subjects did not substantially change the effect estimates (data not shown). Subjects with teeth and severe periodontal disease continued to have the highest cardiorenal mortality rates, suggesting that the extent of this misclassification was small.

The prevalence of periodontal disease is high in Pima Indians, even before the onset of diabetes (1,2); diabetes further increases the risk of periodontal disease (1–3,31). Diabetes is a strong, independent risk factor for CVD, and it is noteworthy that the death rate from cardiorenal diseases among diabetic subjects with no or mild periodontal disease was 0. The death rate from cardiorenal disease did increase significantly, however, with increasing severity of periodontal disease (P trend < 0.01). On the other hand, periodontal disease and CVD have many common risk factors, which could lead to a noncausal association. Common risk factors include diabetes, age, smoking, health behaviors and habits, socioeconomic status, diet, and access to care (32). Nevertheless, in this study of individuals with diabetes, the relationship between periodontal disease and CVD remained significant after accounting for many of these shared risk factors. However, we cannot exclude the potential for confounding by unmeasured risk factors. Socioeconomic status, which may influence health care, was not evaluated in this study. There was also no estimate of diet. However, the extent to which socioeconomic status influences access to health care in this population may be less than in other populations, because medical and dental care is provided to all community members at no cost.

Of the study population, ~19% of subjects were excluded from the analysis due to missing values. Nevertheless, the mortality rates for cardiorenal deaths and all other causes of death for the excluded 19% were not significantly different from the rest of the population included in this study.

The association between periodontal disease and CVD has been reviewed extensively (33). Inflammation associated with periodontal disease may play a central role in the pathogenesis of CVD (34). As with other chronic infections, chronic periodontal disease is associated with systemic changes in blood and blood-forming organs, which may result in activation of markers of inflammation and acute-phase proteins such as C-reactive protein (34). Studies of periodontal disease and CVD or of diabetes and CVD that focus on inflammation are limited by the nonspecific nature of existing markers and the inability of most studies to distinguish acute inflammation from chronic low-grade inflammation. However, despite these limitations, there is remarkable consistency in the findings from a number of studies on the relationship between markers of inflammation, abnormalities of glucose metabolism, and CVD (35). Studies of diabetes and CVD suggest that low-level, chronic inflammation is associated with endothelial dysfunction (35), a pathway potentially linking diabetes and periodontal disease to CVD.

In summary, periodontal disease is a major public health burden in Pima Indians, and it is a strong predictor of death from cardiorenal disease in those with type 2 diabetes. Most cardiorenal deaths were attributable to periodontal disease exposure, and this proportion was remarkably high in younger age-groups.

The effect of periodontal disease is in addition to the effects of traditional risk factors for these diseases. Whether prevention or treatment of periodontal disease can reduce the death rate from either disease, however, remains to be determined.

Acknowledgments— This study was supported in part by USPHS Grant DE-06514 from the National Institute of Dental Research.

We thank the members of the Gila River Indian Community for participation in this investigation. We also thank the physicians and technical staff of the Diabetes Epidemiology and Clinical Research Section, National Institute of Diabetes and Digestive Kidney Diseases, for conducting the diabetes examinations and processing the diabetes data.

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