Periodontal Status and A1C Change

Longitudinal results from the Study of Health in Pomerania (SHIP)

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OBJECTIVE — Infection may be a type 2 diabetes risk factor. Periodontal disease is a chronic infection. We hypothesized that periodontal disease was related to A1C progression in diabetes-free participants.

RESEARCH DESIGN AND METHODS — The Study of Health in Pomerania (SHIP) is a population-based cohort in Germany including 2,973 diabetes-free participants (53% women; aged 20–81 years). Participants were categorized into four groups according to increasing baseline periodontal disease levels (percentage of sites per mouth with attachment loss ≥5 mm, determined a priori); sample sizes for each respective category were 1,122, 488, 463, and 479 (241 participants were edentulous). Mean absolute changes (year 5 minus baseline) in A1C (ΔA1C) were regressed across periodontal categories while adjusting for confounders (e.g., age, sex, smoking, obesity, physical activity, and family history).

RESULTS — Across baseline periodontal disease categories, ΔA1C ± SEM values were 0.023 ± 0.02, 0.023 ± 0.02, 0.065 ± 0.03, and 0.106 ± 0.03 (P_{trend} = 0.02), yielding an approximate fivefold increase in the absolute difference in ΔA1C when dentate participants in the highest versus lowest periodontal disease category were compared; these results were markedly stronger among participants with high-sensitivity C-reactive protein ≥1.0 mg/l ($P_{interaction}$ = 0.01). When individuals who had neither baseline periodontal disease nor deterioration in periodontal status at 5 years were compared with individuals with both poor baseline periodontal health and longitudinal periodontal deterioration, mean ΔA1C values were 0.005 vs. 0.143% (P = 0.003).

CONCLUSIONS — Periodontal disease was associated with 5-year A1C progression, which was similar to that observed for a 2-SD increase in either waist-to-hip ratio or age in this population.

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Chronic infections are a potentially novel risk factor for diabetogenesis (1). Specifically, there is a known association between periodontal infections and type 2 diabetes, although the temporality and mechanisms of this association remain uncertain (2).

To examine the temporality of this association, data from the First National Health and Nutrition Examination Survey (NHANES I) were recently analyzed to explore whether baseline clinical periodontal status predicted incident diabetes among 9,296 initially diabetes-free participants (1). It was reported that baseline periodontal status was a strong predictor of incident diabetes during 20 years of longitudinal follow-up. However, the absence of laboratory A1C or fasting plasma glucose assessments in NHANES I data precluded examination of the influence of periodontal status on glycemia. Consequently, the potential for a diagnostic bias remained; i.e., undiagnosed diabetes might have preceded (and caused) baseline periodontal disease but was subsequently diagnosed and erroneously defined as incident.

To enable a more precise delineation of the natural history of associations between periodontal infections and diabetogenesis, we examined whether baseline clinical periodontal status is associated with 5-year A1C progression among diabetes-free individuals. We tested this hypothesis among participants in the Study of Health in Pomerania (SHIP).

RESEARCH DESIGN AND METHODS

— SHIP is a population-based prospective cohort in East Germany involving the cities of Greifswald, Stralsund, and Anklam and 29 surrounding villages; the 1995 population in this catchment area was 212,157. From each of these cities, German subjects with main residency in the area were randomly drawn, proportional to each community population and stratified by age and sex. A representative sample of 7,008 adults aged 20–79 years were invited to participate. This two-stage cluster sampling method was adopted from the Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) Project, Augsburg, Germany, and yielded 12 5-year age strata (20–81 years) for both sexes. After removal of 746 individuals (126 died, 615 moved away, and 5 had severe medical problems), 6,262 inhabitants were invited. The final sample included 4,310 individuals, yielding a 68.8% participation rate (3). There were 130 passive nonrespondents due to migration and 231 deceased subjects between the two examinations. Of the remaining 3,949 eligible individuals, 649 were active nonrespondents and 3,300 subjects were reexamined, resulting in an 83.6% follow-up rate (4). Participants were excluded from the current analysis if

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they had *1*) prevalent baseline diabetes ($n = 219$), defined as either self-report, physician-diagnosed, or A1C ≥6.5%; *2*) missing A1C ($n = 74$); *3*) missing periodontal data ($n = 136$) (5); or *4*) missing confounder data ($n = 78$). The current analysis included 2,793 participants.

The study was approved by the institutional review board of the University of Greifswald. All participants provided written informed consent.

Oral examination

Calibrated licensed dentists performed the oral examinations, including a full-mouth tooth count. In SHIP-0 the periodontal probe PCP 11 (Hu-Friedy, Chicago, IL) and in SHIP-1 the periodontal probe PCP 2 (Hu-Friedy) were used to assess periodontal probing depth (PPD) and clinical attachment loss for examined teeth. Measurements were taken at four sites per tooth (mesiobuccal, midbuccal, distobuccal, and midlingual), using the half-mouth method on the right or left side in alternate subjects. On the same teeth, coronal caries were scored visually and with the periodontal probe. Caries and missing teeth were registered by surface and the decayed/filled teeth (DFT) index was calculated according to World Health Organization criteria. Yearly calibration exercises (6) yielded an intraclass correlation of 0.82–0.91 per examiner and an interrater correlation of 0.84 relative to attachment loss.

A1C measurement

Nonfasting blood samples were analyzed at one laboratory that participated in the official Germany INSTAND round-robin tests for quality assurance in analytical laboratories, at least semiannually, and internal quality controls were measured daily. At both visits, A1C was measured by cation-exchange chromatography (high-performance liquid chromatography) with spectrophotometric detection (Diamat analyzer; BioRad, Munich, Germany) and a coefficient of variation of 1.5%.

Risk factor assessment

Participants were queried by computer-aided face-to-face interviews on sociodemographic characteristics, medical histories, and medication use, i.e., antidiabetes drugs (Anatomical Therapeutic Chemical [ATC] code A10) and corticoid drugs (ATC codes A01AC, A07EA, D07, D10AA, G01B, H02, M01BA, and R01AD). A self-administered questionnaire assessed region (rural versus urban) and education level (<10, 10, or >10 years of schooling). Leisure-time physical activity was reported as >2, 1–2, or <1 h/week or no activity and was then converted into METs (7). Smoking behavior was assessed with a validated questionnaire and categorized as never/occasional, former, or current smoker (7). Family history of diabetes was determined by asking whether parents or siblings had diabetes.

Height and weight were determined using calibrated scales. Waist circumference was measured at the narrowest place between the last rib and the highest part of the abdomen. Hip circumference was determined as the greatest circumference between the highest point of the iliac crest and the crotch.

Blood pressure was measured three times using a calibrated semiautomatic sphygmomanometer (HEM-705CP; Omron, Tokyo, Japan). The average of the last two measurements was used for analysis.

High-sensitivity C-reactive protein (hs-CRP) was determined in serum by particle-enhanced immunonephelometry (hs-CRP kit; Dade Behring, Deerfield, IL) with a test sensitivity of 0.2 mg/l. Triglycerides were determined enzymatically using reagents from Roche Diagnostics (Hitachi 717; Roche Diagnostics, Mannheim, Germany). Plasma fibrinogen concentrations were assayed according to Clauss using an Electra 1600 analyzer (Instrumentation Laboratory, Barcelona, Spain). White blood cell (WBC) count was measured by the impedance measurement method using the Coulter principle (Coulter MaxM; Coulter Electronics, Miami, FL).

Statistical analysis

Analyses were performed using SAS for Windows (version 9.2; SAS Institute, Cary, NC). PROC SURVEYREG was used to generate variance estimates appropriate for the clustered design.

Periodontal categorizations were created to provide a meaningful contrast in exposure while maintaining reasonable sample size balance across categories. The primary exposure variable was the percentage of periodontal sites with attachment loss (AL) ≥5 mm at baseline (%AL ≥5 mm), which was determined a priori (5). Dentate participants were categorized into four groups based on %AL ≥5 mm as follows: *1*) 1,122 participants without any 5-mm attachment loss who were considered periodontally "healthy" (ALI); 2) 488 participants with %AL ≥5 mm, ranging from 1 to 8% (ALII); 3) 463 participants with %AL ≥5 mm, ranging from 9 to 33% (ALIII); *4*) 479 participants with %AL ≥5 mm, ranging from 34 to 100% (ALIV); and *5*) 241 edentulous participants formed a fifth category (7,8).

Three alternate periodontal exposure definitions were also considered. First, baseline mean PPD was categorized into four groups as follows: *1*) 1.04 ≤ mean PPD ≤ 2.00 mm (PPDI); *2*) 2.01 ≤ mean PPD ≤2.34 mm (PPDII); *3*) 2.35 ≤ mean PPD ≤ 2.75 mm (PPDIII); and *4*) 2.76 ≤ mean PPD ≤ 7.25 mm (PPDIV). Second, dentate participants were categorized into tooth count tertiles (26–28, 21–25, and 1–20 teeth); edentulous participants formed a fourth category. Finally, dentate participants with longitudinal periodontal data were categorized into four groups according to 5-year change (follow-up − baseline) in the percentage of sites with attachment loss ≥5 mm (Δ%AL ≥5 mm) as follows: *1*) ΔALI: 565 participants with improving periodontal health (Δ%AL ≥5 mm < 0); *2*) ΔALII: 887 participants without any change in periodontal status (Δ%AL ≥5 mm = 0); *3*) ΔALIII: 423 participants with Δ%AL ≥5 mm, ranging from 1 to 8%; and *4*) ΔALIV: 437 participants with Δ%AL ≥5 mm, ranging from 9 to 100%. To address the specificity of any observed associations to periodontal infection, we also assessed the association between percentage of decayed/filled teeth (%DFT) and A1C change.

Multivariable linear regression models were used to examine the association between periodontal status (baseline and/or change) and absolute 5-year A1C change (ΔA1C) (calculated as year 5 %A1C − baseline %A1C). Subgroup analyses were performed, removing extreme A1C changes to reduce the potential for biased statistical inferences due to possible ΔA1C normality violations. To reduce the potential for age-related confounding, we also performed stratified analyses in three age strata defined by 20-year age ranges (20–39, 40–59, and ≥60 years). Interaction models assessed the statistical evidence of effect modification between periodontal status and systemic inflammatory variables.

RESULTS

General characteristics

Participants were Caucasian, aged 48 ± 15 years (mean ± SD), and 53% female. Baseline periodontal disease (%AL ≥5 mm) was highly correlated with age ($r = 0.50$, $P < 0.0001$) and was associated with several sociodemographic, behavior/

Table 1—*Characteristics across categories of periodontal disease (%AL ≥5 mm), adjusted for age and sex: SHIP, 1997–2006*

	ALI (0 ± 0%)*	ALII (4 ± 2%)*	ALIII (18 ± 7%)*	ALIV (62 ± 21%)*	Edentulous
n	1,122	489	463	479	241
Sociodemographic					
Age†	38 ± 0.3	47 ± 0.5	53 ± 0.5	59 ± 0.5	68 ± 0.7
Female sex†	61	50	51	40	48
<9 years education	26	25	34	44	53
9–10 years education‡	49	53	51	45	41
>10 years education†	25	22	15	11	6
Lifestyle and behavioral					
Former smokers†	38	36	29	29	28
Current smokers†	13	24	31	42	42
Pack-years smoking†	5 ± 0.4	7 ± 0.6	9 ± 0.6	13 ± 0.6	13.0 ± 0.9
Physical activity (METs/day)	1,900 ± 28	1,950 ± 37	1,907 ± 38	1,893 ± 40	1,797 ± 59
Region (urban vs. rural)‡	63	63	62	54	50
Medical					
BMI (kg/m^2)	26.7 ± 0.15	26.8 ± 0.19	27.2 ± 0.20	27.3 ± 0.21	27.1 ± 0.31
WHR†	0.85 ± 0.002	0.86 ± 0.003	0.87 ± 0.003	0.87 ± 0.003	0.86 ± 0.004
Systolic blood pressure (mmHg)‡	133 ± 0.6	135 ± 0.8	134 ± 0.8	135 ± 0.9	138 ± 1.3
Diastolic blood pressure (mmHg)†	83 ± 0.4	85 ± 0.5	85 ± 0.5	84 ± 0.5	82 ± 0.8
A1C (%)‡	5.20 ± 0.02	5.23 ± 0.02	5.28 ± 0.02	5.25 ± 0.03	5.31 ± 0.04
Triglycerides (mmol/l)*	1.65 ± 0.05	1.83 ± 0.06	1.95 ± 0.06	1.91 ± 0.07	1.76 ± 0.10
WBC count†	6.2 ± 0.07	6.6 ± 0.09	7.0 ± 0.09	6.9 ± 0.09	6.9 ± 0.14
Fibrinogen (g/l)†	2.84 ± 0.02	2.87 ± 0.03	3.00 ± 0.03	3.07 ± 0.03	3.13 ± 0.05
hs-CRP (mg/l)†	2.37 ± 0.15	2.13 ± 0.20	2.47 ± 0.21	3.19 ± 0.21	3.00 ± 0.31
Corticosteroid use	2	2	2	2	2
Family history of diabetes‡	26	34	33	33	27
Dental					
Mean attachment loss (mm)†	1.4 ± 0.03	2.1 ± 0.04	3.0 ± 0.04	5.0 ± 0.04	NA
Mean PPD (mm)†	2.1 ± 0.02	2.3 ± 0.02	2.7 ± 0.03	3.3 ± 0.03	NA
Decayed, filled teeth (*n*)†	6.1 ± 0.08	6.2 ± 0.11	5.6 ± 0.12	4.1 ± 0.12	—§
Decayed, filled surfaces (*n*)†	17.3 ± 0.3	16.6 ± 0.4	14.7 ± 0.4	10.6 ± 0.5	—
Tooth count†	22.6 ± 0.2	23.5 ± 0.2	21.5 ± 0.2	16.4 ± 0.2	—

Data are means ± SEM or %. *Unadjusted category-specific value for attachment loss ≥ 5 mm. †$P < 0.01$. ‡$P < 0.05$. §Edentulous individuals were excluded from specified age- and sex-adjusted regressions because the value of these dependent variables are perfectly correlated with edentulism. NA, not available.

lifestyle, and medical variables (Table 1). Among dentate participants, the mean number of teeth (excluding third molars) was 21 ± 6 after age adjustment. On average, 17% of sites per mouth had attachment loss ≥5 mm, which was higher among men (18%) than among women (13%) ($P < 0.0001$).

Among participants with longitudinal periodontal measures ($n = 2,312$), mean absolute 5-year change in %AL ≥5 mm was 2.3 ± 14% ($P < 0.0001$) with a range of −75 to 70%. Five-year change in mean PPD was −0.08 ± 0.50 mm ($P < 0.0001$). Baseline %AL ≥ 5 mm was weakly and inversely correlated with change in the same variable ($r = −0.05$, $P = 0.008$), whereas baseline mean PPD was positively correlated with 5-year change in %AL ≥ 5 mm ($r = 0.08$, $P = 0.0001$). Men, current smokers, and younger participants were more likely to experience a decline in periodontal health during follow-up. ΔA1C was 0.05 ± 0.59% (range −4.2 to 6.5%); 98% of A1C changes were ≥−1.0% and ≤1.0%. After multivariable adjustment, the following nonperiodontal variables were associated with ΔA1C ($P < 0.05$): waist-to-hip ratio (WHR), fibrinogen, hs-CRP, and former smoking (Table 2).

Baseline periodontal or tooth loss status and A1C change

Participants in the fourth versus first %AL ≥5 mm category experienced an ~0.08% greater 5-year increase in A1C ($P = 0.02$) (Table 3, model 4). ΔA1C was accelerated by ~0.10% among edentulous participants, relative to periodontally healthy participants ($P = 0.05$). When ΔA1C was compared between participants in the fourth versus first attachment loss category among those aged 20–39 years, the absolute difference was 0.08% ($P = 0.04$). Findings were consistent among participants aged 40–59 years (0.10%, $P = 0.005$) and those aged ≥60 years (0.07%, $P = 0.27$). There was evidence for an interaction between %AL ≥5 mm and hs-CRP ($P_{interaction} = 0.01$), in which the increase in ΔA1C with higher %AL ≥5 mm was stronger among participants with hs-CRP ≥1.0 mg/l than in those with hs-CRP <1.0 mg/l (Fig. 1). Trends were consistent when fibrinogen was considered as the effect modifier ($P_{interaction} = 0.24$) but less clear for WBC count ($P_{interaction} = 0.66$) as shown in Fig. 1.

Respective ΔA1C changes in the first to fourth quartiles of mean PPD were −0.001, 0.050, 0.033, and 0.107% ($P_{trend} < 0.01$ after multivariable adjustment as in Table 3, model 4). Mean A1C changes across four categories of baseline tooth count were 0.09% (26–28 teeth),

Table 2—*Five-year A1C change estimates derived from multivariable regression modeling: SHIP, 1997–2006*

Variable	SD	ΔA1C estimate*	*P* value†
Age (years)	15 (years)	0.034	0.12
WHR	0.09	0.049	0.003
Systolic blood pressure (mmHg)	20	0.01	0.38
Triglycerides (mmol/l)	1.34	0.016	0.28
Physical activity (METs)	870	−0.011	0.12
WBC count			
Quartile 1		Reference	
Quartile 2		0.047	0.16
Quartile 3		0.013	0.83
Quartile 4		0.011	0.86
Fibrinogen			
Quartile 1		Reference	
Quartile 2		0.055	0.15
Quartile 3		0.052	0.27
Quartile 4		0.119	0.02
hs-CRP <1.0 mg/l		Reference	
1.0 ≤ hs-CRP <3.0 mg/l		0.060	0.0001
hs-CRP ≥3.0 mg/l		0.033	0.23
Periodontal status‡			
0		Reference	
1–8		−0.004	0.87
9–33		0.020	0.30
34–100		0.093	0.001
Edentulous		0.071	0.26
Sex			
Female		Reference	
Male		−0.002	0.92
Region			
Urban		Reference	
Rural		0.075	0.30
Smoking status			
Never, occasional		Reference	
Former		−0.069	0.002
Current		−0.053	0.25
Educational level			
≥10 years		Reference	
10 years		0.055	0.28
<10 years		0.036	0.72
Family history of diabetes (reference = no history)		0.041	0.08

*Estimates correspond to a 1-SD increase in continuous variables or a change relative to the reference category. Results are simultaneously adjusted for all variables included in the table. Participants missing data for either family history of diabetes, fibrinogen, WBC count, hs-CRP, or hs-CRP >10.0 mg/l were excluded (n = 569). †Significance levels account for the stratified, clustered sampling design in SHIP. ‡The percentage of sites per mouth with attachment loss ≥5 mm.

0.04% (21–25 teeth), 0.02% (1–20 teeth), and 0.07% (edentulous) (P_{trend} = 0.84).

Longitudinal changes in periodontal status and A1C change

Five-year change in %AL ≥5 mm (ΔAL) was associated with ΔA1C (supplementary Figure A3, available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1778/DC1). When individuals who were periodontally healthy at both baseline and follow-up were compared with individuals who had poor baseline periodontal health combined with periodontal deterioration during follow-up (ALIV and ΔALIV), the respective mean A1C changes in the two groups were 0.005 vs. 0.143% (P = 0.003). Five-year change in mean PPD was not associated with ΔA1C; ΔA1C values across categories of mean PPD change were 0.03, 0.06, 0.04, and 0.01%, respectively (P_{trend} = 0.46).

%DFT and A1C change

The %DFT was not correlated with %AL ≥ 5mm (r = −0.02, P = 0.36). After multivariable adjustment, A1C progression across quartiles of %DFT was 0.06, 0.02, 0.05, and 0.03% (P_{trend} = 0.70).

CONCLUSIONS — This is the first study to report that a chronic infection predicts progression of A1C among diabetes-free individuals. We report a positive association between clinical periodontal status and 5-year A1C change among German participants in SHIP. When compared with participants considered periodontally healthy, those participants with elevated levels of baseline periodontal disease experienced an approximate 0.08% greater increase in ΔA1C during 5 years of follow-up. Deteriorating periodontal health during follow-up was also associated with greater increases in ΔA1C. There was evidence of an additive effect of baseline and follow-up periodontal status such that participants with severe baseline periodontal disease coupled with large declines in longitudinal periodontal health experienced an ~0.13% greater increase in 5-year ΔA1C relative to participants who were periodontal healthy at both baseline and follow-up. In addition, the association between periodontal status and ΔA1C was strongest among participants with elevated levels of hs-CRP.

These findings remained after comprehensive adjustment for confounders, which minimized the potential for spurious associations arising from behavioral/lifestyle variations across periodontal disease levels. The results from multivariable models suggest that age was a strong confounder, whereas other covariates had only minimal impact on the results. Additional analyses within age strata were consistent with results from regression models in the full sample and further minimized the potential for age-related confounding.

These data advance previous findings from NHANES I, in which elevated levels of baseline periodontal disease were associated with an approximate twofold increase in incident diabetes risk (1). Specifically, our data demonstrate a temporal trend in which periodontal disease predicts an accelerated longitudinal change in A1C after control for baseline

Table 3—*A1C change across increasing categories of baseline periodontal disease (of sites with attachment loss ≥5 mm): SHIP, 1997–2006*

Model	ALI (0 ± 0%)*	ALII (4 ± 2%)*	ALIII (18 ± 7%)*	ALIV (62 ± 21%)*	Edentulous	*P* value†
n	1,122	488	463	479	241	
1	−0.035 ± 0.017	0.017 ± 0.026	0.097 ± 0.025	0.162 ± 0.029	0.225 ± 0.047	<0.001
2	0.017 ± 0.018	0.022 ± 0.026	0.071 ± 0.026	0.109 ± 0.030	0.130 ± 0.051	0.009
3	0.020 ± 0.018	0.023 ± 0.026	0.064 ± 0.026	0.105 ± 0.030	0.136 ± 0.050	0.013
4	0.023 ± 0.018	0.023 ± 0.027	0.065 ± 0.026	0.106 ± 0.030	0.124 ± 0.052	0.025
5	0.020 ± 0.017	0.020 ± 0.024	0.080 ± 0.022	0.090 ± 0.028	0.143 ± 0.048	0.011
6	0.032 ± 0.039	0.029 ± 0.035	0.043 ± 0.040	0.107 ± 0.042	0.110 ± 0.073	0.02
7	0.024 ± 0.026	0.021 ± 0.031	0.045 ± 0.029	0.117 ± 0.040	0.100 ± 0.052	<0.05
8	0.012 ± 0.018	0.019 ± 0.023	0.071 ± 0.026	0.098 ± 0.026	0.101 ± 0.043	0.013
9	0.012 ± 0.017	0.014 ± 0.022	0.061 ± 0.024	0.088 ± 0.026	0.071 ± 0.041	0.038
10	−0.022 ± 0.015	−0.012 ± 0.019	0.039 ± 0.022	0.068 ± 0.022	0.031 ± 0.034	0.008

Data are means ± SEM. Model 1: unadjusted. Model 2: adjusted for age, sex, and region. Model 3: model 2 + smoking and WHR. Model 4: model 3 + education, systolic blood pressure, triglycerides, and physical activity ($n = 10$ participants excluded because of missing triglyceride data). Model 5: model 4 + natural log of baseline A1C. Model 6: model 4 + hs-CRP, WBC count, fibrinogen, and corticosteroid use ($n = 146$ participants excluded because of missing data on hs-CRP, WBC count, or fibrinogen; additional $n = 78$ excluded due to hs-CRP >10 mg/l). Model 7: model 6 + family history of diabetes (parent or sibling; $n = 408$ participants excluded because of uncertain family history) ($n = 54$ participants reported corticosteroid use). Model 8: model 4 adjustments removing $n = 8$ participants with A1C change <−3.0 or >3.0. Model 9: model 4 adjustments removing $n = 21$ participants with A1C change <−2.0 or >2.0. Model 10: model 4 adjustments removing $n = 157$ participants with A1C change <−1.0 or >1.0. *Category-specific value for adjustment loss ≥5 mm. †*P* value for linear trend across dentate participants. All SEMs and significance levels account for the stratified, clustered sampling design in SHIP.

A1C levels and among participants deemed to be diabetes free at baseline using a standardized diabetes definition. This result greatly minimizes the possibility that elevated blood glucose levels were present before and therefore contributed to periodontal disease observed at baseline.

The hypothesis that periodontal infections can influence diabetogenesis is biologically plausible, and the concept of inflammation-mediated insulin resistance is intriguing (9). Animal models have demonstrated that virulence factors secreted by periodontal pathogens can stimulate production of inflammatory cytokines such as tumor necrosis factor-α (10). Human studies from this population (11) and others (12) support the notion that periodontal infections can induce a state of low-grade chronic inflammation, and periodontal therapy has been shown to decrease systemic inflammation (13). Accordingly, tumor necrosis factor-α can induce a state of insulin resistance (14), and systemic inflammation has also emerged as a novel predictor of incident diabetes (15,16).

The fact that inflammatory adjustments did not remove the association between periodontal status and ΔA1C suggests that these variables might be sufficient but not necessary mediators in the hypothesized causal path between infection and diabetogenesis (17). Alternatively, the observation of a potential interaction between periodontal status and hs-CRP supports the notion that a synergistic combination of both oral infection and systemic immune response, as opposed to a localized oral infection alone, might be necessary for relevant metabolic abnormalities to develop. These subgroup findings require confirmation in other populations.

The observed ~0.08% difference in 5-year A1C progression between high and low levels of periodontal disease is potentially clinically relevant. This difference was similar to that observed for a 2-SD increase in either WHR or age in this population. Moreover, the difference in ΔA1C is on the same order of magnitude as that reported previously for intervention studies from the Diabetes Prevention Program Research Group (DPPRG) (18). The DPPRG observed an ~0.15% reduction in ΔA1C over 4 years among diabetes-free participants receiving either metformin or lifestyle modification relative to participants receiving placebo; these A1C findings translated into either a 31% (metformin) or 58% (lifestyle modification) reduction in incident diabetes.

We have used clinical attachment loss as an indirect surrogate of cumulative exposure to a specific array of chronic infections. Future studies with periodontal bacterial measures and/or a broader range of chronic infection assessment can clarify the nature of associations between infection and diabetogenesis; these approaches have been illuminating for cardiovascular disease (19,20). Data on the association between periodontal status and fasting blood glucose levels can further inform our current findings, which were limited to A1C.

The finding that caries were not associated with ΔA1C enhances the specificity of the oral infection hypothesis. Although caries also have a bacterial etiology, they are not typically known to influence systemic inflammation (21).

The observation that edentulous participants demonstrated mean A1C increases similar to those of dentate participants with periodontal disease might appear counterintuitive to the concept of systemic risk induced by bacterial biofilms on tooth surfaces. However, these findings are consistent with those of others who have shown edentulous participants to be at elevated risk for atherosclerosis (7,8), hypertension (22), and diabetes (1). Desvarieux et al. (8) have suggested that once infection-induced systemic damage has occurred, it is not entirely reversible. Alternatively, systemic inflammation related to oral infections might not abate after resolution of clinical disease. It is also possible that repeated bacteremic events occurring before extraction of periodontally affected teeth (23) might allow oral pathogens to colonize systemically. Indeed, viable oral pathogens have been identified in atheromatous plaques (24). Therefore, once bacterial species have colonized the host, tooth extraction, by itself, should not affect their future viability and/or pathogenicity. Although these concepts are speculative and cannot be tested in the current study, they are biologically plau-

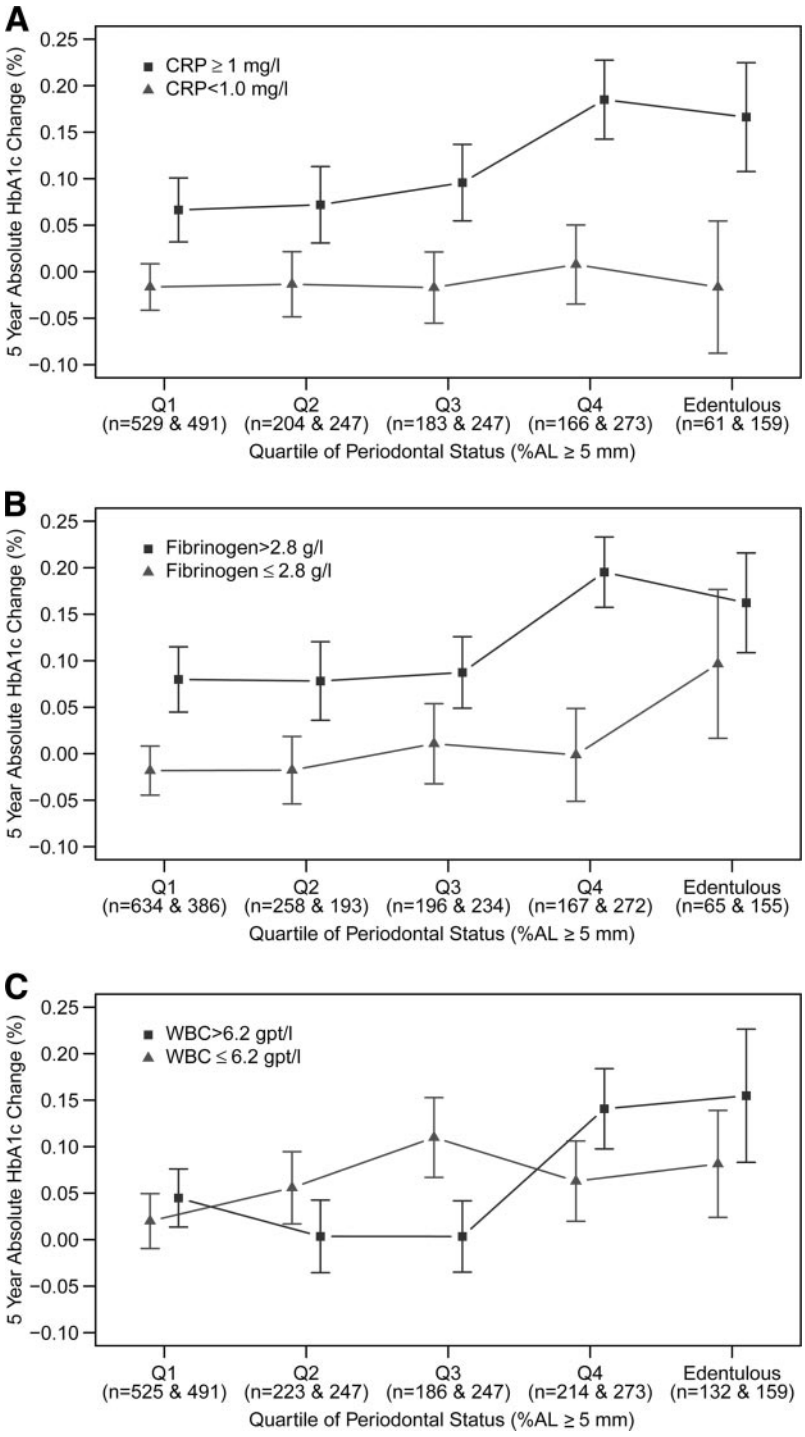

Figure 1—*Mean 5-year A1C changes across categories of baseline clinical periodontal status according to levels of systemic inflammation: SHIP, 1997–2006. All results were adjusted for age, sex, region, smoking, BMI, education, systolic blood pressure, triglycerides, physical activity, corticosteroid use, hs-CRP, WBC count, and fibrinogen. Sample sizes are presented with* x*-axis category labels as low and high inflammation groups, respectively.* A*: hs-CRP,* $P_{interaction} = 0.01$*;* P *value for linear trend across periodontal category among dentate participants with high CRP = 0.05;* P *value for linear trend across periodontal category among dentate participants with low CRP = 0.73.* B*: Fibrinogen,* $P_{interaction} = 0.24$*;* P *value for linear trend across periodontal category among dentate participants with high fibrinogen = 0.06;* P *value for linear trend across periodontal category among dentate participants with low fibrinogen = 0.63.* C*: WBC count,* $P_{interaction} = 0.66$*;* P *value for linear trend across periodontal category among dentate participants with high WBC count = 0.25;* P *value for linear trend across periodontal category among dentate participants with low WBC count = 0.24.*

sible and consistent with the published literature.

We have found elevated levels of periodontal disease, as well as progression of periodontal disease, to be predictors of A1C progression in a randomly sampled, population-based study of Germans over 5 years of follow-up. These data support the hypothesis that chronic infections might contribute to diabetogenesis. We await longitudinal results from year 10 in SHIP, which will allow us to determine whether these subclinical A1C changes translate into increased risk for incident diabetes. Focused intervention studies will be necessary to make definitive causal inference regarding the potential role of anti-infective therapy in reducing the risk of diabetes. If confirmed, this relationship would be of substantial public health importance, given the population prevalence of periodontal infections (25) and the availability of effective periodontal disease therapies.

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