



Non-linear association of periodontal pathogen antibodies with mortality



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ABSTRACT

Background: Periodontal pathogens are associated with predisposition to chronic diseases and death. Antibody levels against them reflect flora burden, although high levels might indicate a protective response. We studied all-cause and cause specific mortality in relation to antibody levels in a representative US sample.

Methods: Adults ≥ 20 years ($n = 6993$) from the second phase of the Third National Health and Nutrition Examination Survey (NHANES III) were followed for a median of 13.2 years. Serum antibodies against *Porphyromonas gingivalis* (antiPG) and *Actinobacillus actinomycetemcomitans* (antiAA) were quantified by ELISA at baseline (1991–1994). Mortality hazard ratios (HRs) were calculated across antibody quartiles using the quartile with highest mortality as reference.

Results: Median (25th, 75th percentiles) antiPG was 72 (63, 93) ELISA Units (EU) and median antiAA was 70 (64, 89) EU. After adjustment for potential confounders, mortality was highest for participants with antibodies in the third antiPG quartile (72–92 EU), with lower mortality risk for values not only below but also above this range [HR for the 1st to 4th quartiles: 0.81 (95% CI: 0.65, 1.01), 0.67 (95% CI: 0.55, 0.82), 1.00 (Reference), 0.79 (95% CI: 0.64, 0.97)]. In spline regression models the association had an inverted U-shape and mortality exhibited a peak at 84 EU (67th percentile). Mortality was not associated with antiAA.

Conclusions: Mortality was highest for those just above the median antiPG and a reduced risk was present among those with low or high levels of the antibody. Future studies should confirm this downward trend in upper levels and investigate a potential protective role of immunity against *P. gingivalis*.

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1. Introduction

Periodontitis is a chronic oral infection caused by pathogens from the oral biofilm [1–3]. The percentage of people who have been exposed to periodontal pathogens is high, increases with age, and shows a first noticeable rise during adolescence [3,4].

Periodontitis causes a systemic immune response and thus individuals with chronic [5], early-onset [6], and refractory periodontitis [7] present elevated serum antibodies to multiple species [8,9]. In particular, serum antibodies against *Porphyromonas gingivalis* and *Actinobacillus actinomycetemcomitans* – common oral bacteria that cause periodontitis – are elevated among most patients with oral diseases [10]. Interestingly, individuals with very high antibody levels also have lower flora burden [11]. This apparent contradiction may

occur because some antibodies are effectively protective and it suggests that vaccines could be useful for preventing periodontitis [12].

Periodontitis appears together with cardiovascular and other chronic diseases in epidemiological studies: mainly with coronary disease, myocardial infarction [13,14], colorectal and pancreatic cancer [15]. Sfyroeras et al. and Linden et al. showed that subjects with periodontal infection also have an increased risk of stroke [16] and cognitive impairment [17]. Still, there is substantial heterogeneity of results from studies that investigate the association of antibody levels with chronic diseases [18]. The possibility that high levels of antibodies against oral pathogens protect also against chronic diseases has not been previously addressed. Most studies have assumed that the association is linear, expecting increasing disease levels with increasing antibodies and consequently they could not detect changes in the trend for very high antibody levels. In addition, if such change in the trend exists, ignoring it would make it difficult to find an overall association, given that a descending trend for upper antibody levels would counter balance an ascending trend for lower levels.

We investigated whether antibodies against *P. gingivalis* (antiPG) and *A. actinomycetemcomitans* (antiAA) are associated with all-cause

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mortality and mortality from specific causes in adults from a nationally representative US sample, allowing for a possible non-linear association. We hypothesized that not only low levels of these antibodies would be associated with a lower mortality risk but also that very high antibody levels might be protective. Furthermore, we tried to identify whether the lower mortality rate among individuals with very high antibody levels might depend on differences in known cardiovascular risk factors.

2. Methods

The National Center for Health Statistics (NCHS) conducted the second phase of the Third US National Health and Nutrition Examination Survey (NHANES III) between 1991 and 1994 using a complex multi-stage design to sample the civilian non-institutionalized US population [19]. Serum antibodies measurements were available for participants aged 12 years and older who had a dental exam.

We included participants with available serum antibodies and known mortality status with ≥ 20 years of age ($N = 7736$). Of these, participants with all available covariates were included in our analysis ($N = 6993$).

2.1. Antibody levels against periodontal pathogens

Antibodies against *P. gingivalis* (antiPG) and *A. actinomycetemcomitans* (antiAA) were quantified by enzyme-linked immunosorbent assay

(ELISA). Three strains of each bacteria, which were grown by Stanley C. Holt of San Antonio Texas, were pooled for preparation of plates for the screening assays and serum standards were provided by Dr. Ebersol of the University of Texas, San Antonio. Results were reported in ELISA Units (EU) [20].

2.2. Mortality

For each study participant, follow-up extended from the date of their study visit at baseline until their date of death, or December 31, 2006, whichever occurred first. Vital status was ascertained through the National Death Index, and the cause of death was determined on the basis of the underlying cause of death listed on the death certificate [21].

The International Classification of Diseases, Ninth Revision (ICD-9) was used for deaths occurring from 1988 through 1998, and the International Statistical Classification of Diseases, 10th Revision (ICD-10) was used for deaths occurring from 1999 through 2006. In addition to all-cause mortality, we studied deaths due to cardiovascular disease (ICD-9 codes 390 to 434 and 436 to 459, and ICD-10 codes I00 to I99), cancer (ICD-9 codes 140 to 239, and ICD-10 codes C00 to C97 and D00 to D48), and other causes of death (rest of the codes). We used the public-use data file available from the NCHS which yields results comparable to the restricted-use data file [22].

Table 1

Characteristics of the study population, mean antibody levels and crude mortality rates.

	Proportion (%)	AntiPG ^a (EU ^b)	p	AntiAA ^c (EU)	p	Mortality rate (deaths/10 ⁵ person-years)	p
All		83.7		81.4		1168.3	
Age							
<40 years	45.7	78.5	<0.001	79.0	0.005	184.2	<0.001
≥ 40 and < 60 years	32.3	86.9		82.4		590.6	
≥ 60 years	22.0	90.5		85.3		4926.9	
Gender							
Male	47.9	84.4	0.34	81.4	0.96	1229.9	0.87
Female	52.1	83.0		81.4		1112.2	
Race							
Non-Hispanic White	76.4	77.5	<0.001	76.3	<0.001	1249.2	0.006
Non-Hispanic Black	10.3	114.2		94.4		1259.8	
Mexican-American	5.0	98.4		97.0		618.5	
Others	8.2	104.8		110.6		663.0	
Education							
Less than high school	23.2	90.2	<0.001	86.6	0.001	2271.4	<0.001
Complete high school	33.3	84.2		81.3		1142.3	
More than high school	43.5	80.1		78.9		652.0	
Income Index Ratio							
<2	34.0	91.4	<0.001	83.9	0.05	1650.8	0.03
≥ 2 and <4	35.8	81.5		81.2		1099.4	
≥ 4	30.1	78.2		79.0		732.9	
Marital status							
Married at present	67.3	83.0	0.02	81.1	0.69	1032.1	<0.001
Formerly married	17.6	88.8		82.5		2432.8	
Never married	15.1	81.0		81.5		459.1	
Diabetes							
No	92.5	82.9	<0.001	81.3	0.47	994.1	<0.001
Yes	7.5	94.1		83.2		3739.3	
Hypertension							
No	76.2	81.7	<0.001	81.0	0.10	593.9	<0.001
Yes	23.8	90.2		82.7		3314.7	
Hypercholesterolemia							
No	79.4	82.6	0.02	81.4	0.98	977.7	<0.001
Yes	20.6	88.0		81.4		1947.6	
Smoking status							
Never	47.7	86.7	<0.001	84.5	<0.001	895.3	<0.001
Former	26.1	84.4		82.0		1722.2	
Current	26.2	77.9		75.6		1147.3	

Values are survey weighted percentages for categorical characteristics or geometric means for antibody levels. p values are calculated from generalized linear models (linear and Poisson regression as appropriate) accounting for the survey design.

^a AntiPG – serum antibodies against *Porphyromonas gingivalis*.

^b EU – ELISA Units.

^c AntiAA – serum antibodies against *Actinobacillus actinomycetemcomitans*.

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