The Prevalence of Inflammatory Periodontitis Is Negatively Associated with Serum Antioxidant Concentrations

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Abstract

Chronic periodontitis is an inflammatory disease that affects the supporting tissues of the teeth. It is initiated by specific bacteria within the plaque biofilm and progresses due to an abnormal inflammatory-immune response to those bacteria. Periodontitis is the major cause of tooth loss and is also significantly associated with an increased risk of stroke, type-2 diabetes and atheromatous heart disease. Oxidative stress is reported in periodontitis both locally and peripherally (serum), providing potential mechanistic links between periodontitis and systemic inflammatory diseases. It is therefore important to examine serum antioxidant concentrations in periodontal health/disease, both at an individual species and total antioxidant (TAOC) level. To determine whether serum antioxidant concentrations were associated with altered relative risk for periodontitis, we used multiple logistic regression for dual case definitions (both mild and severe disease) of periodontitis in an analysis of 11,480 NHANES III adult participants (>20 y of age). Serum concentrations of vitamin C, bilirubin, and TAOC were inversely associated with periodontitis, the association being stronger in severe disease. Vitamin C and TAOC remained protective in never-smokers. Higher serum antioxidant concentrations were associated with lower odds ratios for severe periodontitis of 0.53 (CI, 0.42,0.68) for vitamin C, 0.65 (0.49,0.93) for bilirubin, and 0.63 (0.47,0.85) for TAOC. In the subpopulation of never-smokers, the protective effect was more pronounced: 0.38 (0.26,0.63, vitamin C) and 0.55 (0.33,0.93, TAOC). Increased serum antioxidant concentrations are associated with a reduced relative risk of periodontitis even in never-smokers. J. Nutr. 137: 657–664, 2007.

Introduction

Chronic periodontitis is an inflammatory disease that affects 10–15% of the developed world population and is the major cause of tooth loss in adults (1). It is initiated by the subgingival plaque biofilm, and tissue destruction appears to be largely mediated by an abnormal host response to specific bacteria and their products (2,3). The aberrant response is characterized by exaggerated inflammation, involving the release of excess proteolytic enzymes (4) and reactive oxygen species (ROS)[3] (3). More recently, periodontitis has been recognized as a risk factor for certain systemic diseases where low-grade inflammation within the peripheral circulation is associated with the etiology of that disease or its progression. Associations have been demonstrated repeatedly between periodontitis and type-2 diabetes (5), cardiovascular and cerebrovascular disease (6,7).

A growing body of evidence implicates oxidative stress in the pathobiology of chronic periodontitis. Several studies demonstrated increased levels of biomarkers for tissue damage, induced by ROS in periodontitis patients relative to controls (8–10). In response to oxidative stress, antioxidant enzymes appear upregulated in inflamed periodontal tissues (9,11) and in gingival crevicular fluid, where levels correlate inversely with pocket depth (12). Furthermore, extracellular antioxidant scavengers are depleted both individually (13) as well as in terms of total antioxidant activity (TAOC) (14,9). Tissue damage arises directly from oxidative stress and also indirectly via activation of redox-sensitive gene transcription factors like nuclear factor κ-B (3), which in turn leads to downstream proinflammatory cytokine/chemokine production (15,16). The resultant periodontal inflammation creates a low grade inflammatory response detectable within the peripheral vasculature (17).

Interest has therefore re-emerged in the relation between antioxidant micronutrients and periodontitis. Studies from the 1970s and 1980s report conflicting results regarding associations between several individual micronutrients and prevalence of periodontitis (18). However, many utilized dietary questionnaires rather than serum biochemistry (19) and intervention studies focused on chronic gingivitis (20,21). The limitations of questionnaire-based approaches to determining antioxidant intake have recently been recognized (22). Food frequency questionnaires deliver weak associations with serum biochemistry (23) in nonsupplement users and only moderate correlations in supplement users (24).

[3] Abbreviations used: HRT hormone replacement therapy; OC oral contraceptive; OR, odds ratio; PIR poverty-income ratio; ROS reactive oxygen species; TAOC total antioxidant capacity.

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More importantly, antioxidants work in concert rather than in isolation, by recycling each other from their oxidized counterparts. Therefore, measuring individual species alone imposes limitations, principally that the total antioxidant capacity of a biological system is not necessarily the sum of the individual antioxidant concentrations, but also that hitherto uncharacterized antioxidants, which may have biological significance, are not accounted for (25). The main limitation of TAOC assays is that they provide very little information on specific mechanisms of radical removal and hence the contribution of individual antioxidant species to the pathogenesis of a disease. For the definitive analysis of large epidemiological datasets that contain measurements of multiple individual serum antioxidants, we developed a predictive model (25) that enables us to derive a measure of serum TAOC (26) from individual antioxidant concentrations. There is currently a lack of data on the relation between both individual serum antioxidant concentrations and the prevalence of periodontitis and between TAOC and periodontitis.

We hypothesize that inverse associations exist between some serum antioxidant concentrations (including TOAC) and the prevalence of periodontitis. The purpose of our study was to evaluate, to our knowledge for the first time, associations between individual serum antioxidant concentrations and periodontitis prevalence and serum total antioxidant capacity and periodontitis using data from the Third National Health and Nutrition Examination Survey (NHANES III).

Methods

Study data and design

The NHANES III survey (1988–1994) examined the health and nutritional status of a civilian noninstitutionalized U.S. population through a complex, multistage, stratified, clustered sample survey. A detailed description of the survey including approval by the Institutional Review Board of the National Center for Health Statistics can be found elsewhere (27). Briefly, periodontal measurements, including probing depths and clinical attachment levels, were performed at the mesiobuccal line angle and midbuccal sites of all teeth except 3rd molars in 2 randomly selected quadrants.

Laboratory assessments

Details of the assays utilized for analyzing individual serum micronutrients are reported elsewhere (27). Serum antioxidants assessed were α-carotene, β-carotene, selenium, lutein, uric acid, β-cryptoxanthine, vitamins A, C, E and bilirubin. Serum TAOC was calculated as the weighted sum of the serum concentrations of uric acid, vitamin A, vitamin C, and vitamin E based on a previously described model (25).

Data on covariates

Respondents were classified as never smokers (<100 lifetime cigarettes), former smokers (≥100 lifetime cigarettes, not currently smoking) or current smokers (≥100 lifetime cigarettes, currently smoking). Current smokers were further categorized by the number of cigarettes smoked per day (up to 10, 11–20, 21–30, and >30/d).

The poverty income ratio (PIR) was computed as the ratio of family income vs. the poverty threshold. Level of education was reported as completed years of education and categorized as <12 y, 12 y, or >12 y. Female respondents reported on the never, former, or current use of oral contraceptives (OC) and hormone replacement therapy (HRT). Diabetes mellitus was reported at the household interview and BMI was derived from body height and weight measurements.

Homocysteine levels were also investigated in this study because it has been implicated in increasing oxidative stress, reducing antioxidant levels, increasing neutrophil production of reactive oxygen species, and increasing vascular adhesion molecule expression, all of which have been cited as important factors in the periodontal lesion. The lack of any positive association with periodontitis was apparent in all models tested and it was therefore not included as a covariate in the multiple regression analysis.

Statistical analysis

Case definitions. As previously proposed at the 5th European Workshop on Periodontal Diseases, we used 2 different definitions of periodontitis representing mild or more advanced periodontitis (28,29). However, because NHANES III utilized probing measurements at the mesiobuccal line angles rather than interproximally, we defined mild periodontitis as previously described for NHANES III as at least one site with both clinical attachment loss ≥4 mm and probing pocket depth of ≥4 mm (30). In addition, we defined severe periodontitis as ≥2 mesiobuccal sites with clinical attachment loss of ≥5mm and ≥1 mesiobuccal sites with probing pocket depth of ≥4 mm (modified from CDC Working Group proposal) (31).

With the exception of PIR and OC/HRT use (missing values coded as "missing"), subjects with missing data for covariates were excluded. Multiple logistic regression was used to evaluate associations between serum antioxidant concentrations and prevalence of chronic periodontitis, adjusting for age, gender, race/ethnicity, BMI, cigarette smoking, OC and HRT use, diabetes, PIR, and education. Serum antioxidant concentrations were modeled as quintiles. Trend tests were performed by entering continuous variables. To facilitate comparability and interpretability of resulting estimates, the serum antioxidant concentrations were standardized to 0 ± 1 (mean ± SD). All models accounted for survey clustering and stratification using the svy-procedures in STATA, version 7.0. We evaluated effect modification by gender and race/ethnicity using interaction terms and also ran separate analyses restricted to never-smokers.

Results

Laboratory and periodontal data were available for 11,895 adults (aged ≥20 y). Four hundred fifteen volunteers (3.5%) were excluded due to missing covariates. The final analytic sample comprised 11,480 individuals. There were 1567 (14%) subjects with mild periodontitis, whereas 609 (5%) individuals had severe periodontitis. In this sample, subjects with periodontitis were older, poorer, and more likely to be male, non-Hispanic black, smoking, diabetic, and more likely to have <12 y of education than subjects without periodontitis. Women with periodontitis were more likely to have never used oral contraceptives or HRT than women without periodontitis (**Table 1**).

Median serum antioxidant concentrations per quintile, along with odds ratios (OR) and 95% CI for mild and severe periodontitis are detailed in **Tables 2 and 3**.

Association between antioxidants and mild periodontitis. In basic models adjusting only for age, gender, race, or ethnicity, significant inverse associations were found between serum concentrations of lycopene, α-carotene, β-carotene, selenium, lutein, β-cryptoxanthine, vitamin C, and bilirubin as well as TAOC and the prevalence of mild periodontitis (Table 2). In the full model these associations were markedly attenuated, with significant inverse associations remaining between periodontitis prevalence and α-carotene, β-carotene, β-cryptoxanthin, vitamin C, bilirubin, and TAOC (Table 2). The strongest association was between serum concentrations of vitamin C and subjects in the highest quintiles having 39% (CI 26, 51) lower odds of periodontitis than subjects in the lowest quintile (trend OR: 0.82, CI 0.76, 0.87, Table 2). In never-smokers, the associations between vitamin C, bilirubin, and TAOC and the prevalence of periodontitis were similar to those in the full sample, but the associations with α- and β-carotene and β-cryptoxanthin were not confirmed among never-smokers. Never-smokers with vitamin C serum concentrations in the upper quintile had 50%

TABLE 1 Distribution of covariates by periodontal disease status defined according to dual case definitions for mild and severe disease[1]

	Mild disease		Severe disease	
Variable	Cases	Non-cases	Cases	Non-cases
n	1567	9913	609	10,871
Age, *y*	52.2 ± 15.6	42.6 ± 17.4	56.4 ± 14.3	43.2 ± 17.4
Gender, *n (%)*				
Male	957 (61.1)	4437 (44.8)	415 (68.1)	4979 (45.8)
Female	610 (38.9)	5476 (55.2)	194 (31.9)	5892 (54.2)
Race/ethnicity, *n (%)*				
Non-Hispanic white	480 (30.6)	3892 (39.3)	197 (32.4)	4175 (38.4)
Non-Hispanic black	580 (37.0)	2656 (26.8)	237 (38.9)	2999 (27.6)
Hispanic	450 (28.7)	2941 (29.7)	154 (25.3)	3237 (29.8)
Other	57 (3.6)	424 (4.3)	21 (3.5)	460 (4.2)
BMI, kg/m^2	27.9 ± 5.9	27.1 ± 5.7	27.6 ± 6.0	27.2 ± 5.8
OC use,[2] *n (%)*				
Never	325 (54.7)	2006 (37.4)	115 (61.9)	2216 (38.4)
Former	251 (42.4)	2724 (50.8)	69 (37.1)	2906 (50.4)
Current	18 (3.0)	634 (11.8)	2 (1.1)	650 (11.3)
HRT use,[2] *n (%)*				
Never	288 (76.4)	1288 (65.6)	100 (78.1)	1476 (66.7)
Former	60 (15.9)	368 (18.8)	21 (16.4)	407 (18.4)
Current	29 (7.7)	307 (15.6)	7 (5.5)	329 (14.9)
Diabetes, *n (%)*				
Yes	191 (12.2)	560 (5.6)	93 (15.3)	658 (6.1)
No	1376 (87.8)	9353 (94.4)	516 (84.7)	10,213 (94.0)
Poverty-income ratio[2]	2.5 ± 1.8	2.1 ± 1.6	2.1 ± 1.6	2.5 ± 1.8
Education, *n (%)*				
<12 y	799 (50.1)	3381 (34.1)	348 (57.1)	3832 (35.3)
12 y	481 (30.7)	3223 (32.5)	164 (26.9)	3540 (32.6)
≥12 y	287 (18.3)	3309 (33.4)	97 (15.9)	3499 (32.2)
Smoking, *n (%)*				
Never	546 (34.9)	5492 (55.4)	170 (27.9)	5862 (53.9)
Former	405 (25.8)	2094 (21.1)	175 (28.7)	2322 (21.4)
Current, *cigarettes/d*				
≤10	262 (16.7)	1207 (12.2)	99 (16.3)	1370 (12.6)
11–20	232 (14.8)	804 (8.1)	106 (17.4)	929 (8.6)
21–30	55 (3.5)	182 (1.8)	28 (4.6)	209 (1.9)
>30	67 (4.3)	144 (1.4)	31 (5.1)	179 (1.7)

[1] Values are means ± SD or n (%).
[2] Variables have missing values.

(95% CI: 36, 70) lower odds of periodontitis than adults in the lowest quintile (trend OR: 0.80, CI 0.71, 0.89) (Table 2).

Association between antioxidants and severe periodontitis. In general the strength or nature of associations for all antioxidants between severe and mild disease did not differ (Tables 2 and 3). Vitamin C concentrations showed the strongest inverse association with severe periodontitis. Subjects in the upper quintile had 47% (CI 32, 58) lower odds of periodontitis than subjects in the lower quintile of serum vitamin C (trend OR: 0.76, CI 0.69, 0.84) (Table 3). Again, among never-smokers, this association was even stronger (OR for upper vs. lower quintile: 0.38; CI 0.26, 0.63). Bilirubin was significantly negatively associated with severe periodontitis prevalence in the full model (Table 3); however, whereas the estimate for linear trend was similar among never-smokers, the odds of severe periodontitis for subjects with bilirubin concentrations in the upper quintile was similar to those in the lowest quintile. For TAOC, subjects in the upper quintile had 37% (CI 15, 53) lower odds of severe periodontitis than subjects in the lower quintile (trend OR: 0.85, CI 0.77, 0.94) and never-smokers had 45% (CI 33, 93) lower odds of severe periodontitis in the upper quintile of TAOC relative to the lowest quintile.

Discussion

Previous studies revealed conflicting data for associations between antioxidant micronutrient intakes and periodontitis as assessed by dietary questionnaires (19,22). Analysis of serum biomarkers augments the interpretation of diet-disease associations over and above information that can be gained from dietary questionnaires alone. Whereas several serum antioxidants demonstrated significant inverse associations with the prevalence of periodontitis for both mild and severe case definitions in age, sex, race, and ethnicity adjusted models, the majority of associations appeared to be explained by other confounding factors, such as diabetes and smoking. Given the complexity of assessing smoking status by self-report and the effects of smoking on various

TABLE 2 OR and 95% CI for prevalence of mild periodontitis by quintile of serum antioxidant concentration

Variable	Quintile[1]	Serum concentration[2]	Subjects, *n*	OR[3]	95% CI	OR[4]	95% CI
Lycopene, *μmol/L*	I	0.19	2451	1	Ref	1	Ref
	II	0.30	2192	0.91	0.74, 1.11	0.86	0.67, 1.11
	III	0.39	2425	0.93	0.78, 1.10	0.87	0.62, 1.23
	IV	0.52	2176	0.89	0.71, 1.12	0.92	0.67, 1.27
	V	0.71	2236	0.88	0.73, 1.07	0.88	0.62, 1.25
	Trend			0.97	0.92, 1.04	1.02	0.92, 1.13
				$P = 0.41$		$P = 0.74$	
α-Carotene, *μmol/L*	I	0.02	2708	1	Ref		
	II	0.06	2845	0.84	0.71, 1.00	0.85	0.64, 1.13
	III	0.07	1750	0.87	0.71, 1.05	0.89	0.66, 1.21
	IV	0.09	2037	0.88	0.71, 1.08	0.93	0.68, 1.27
	V	0.17	2140	0.60	0.46, 0.77	0.71	0.48, 1.05
	Trend			0.92	0.86, 0.98	0.99	0.93, 1.05
				$P = 0.009$		$P = 0.74$	
β-Carotene, *μmol/L*	I	0.11	2358	1	Ref		
	II	0.17	2265	1.00	0.84, 1.20	1.19	0.84, 1.67
	III	0.26	2462	0.96	0.81, 1.16	1.09	0.80, 1.49
	IV	0.41	2238	0.81	0.69, 0.95	1.07	0.76, 1.47
	V	0.73	2157	0.80	0.65, 0.98	0.99	0.73, 1.35
	Trend			0.87	0.82, 0.93	0.92	0.85, 1.00
				$P = 0.0001$		$P = 0.044$	
Selenium, *nmol/L*	I	1.32	2396	1	Ref		
	II	1.46	2185	1.14	0.97, 1.34	1.14	0.92, 1.40
	III	1.55	2352	1.06	0.90, 1.24	0.99	0.76, 1.28
	IV	1.66	2325	1.01	0.84, 1.22	1.23	0.93, 1.63
	V	1.83	2131	0.93	0.76, 1.14	0.90	0.64, 1.26
	Trend			0.96	0.90, 1.02	0.96	0.88, 1.05
				$P = 0.15$		$P = 0.38$	
Lutein, *μmol/L*	I	0.21	2647	1	Ref		
	II	0.30	2078	1.01	0.85, 1.20	1.00	0.74, 1.35
	III	0.37	2312	1.12	0.94, 1.32	1.15	0.83, 1.60
	IV	0.47	2333	1.02	0.83, 1.25	1.00	0.73, 1.37
	V	0.69	2110	1.01	0.83, 1.23	1.01	0.83, 1.48
	Trend			0.26	0.98, 1.09	1.06	0.99, 1.12
				$P = 0.26$		$P = 0.09$	
Uric acid, *μmol/L*	I	208.2	2375	1	Ref		
	II	267.7	2288	0.94	0.78, 1.13	0.76	0.56, 1.02
	III	309.3	2410	1.04	0.87, 1.24	0.85	0.65, 1.12
	IV	362.8	2194	1.00	0.81, 1.24	1.01	0.72, 1.41
	V	434.2	2213	0.92	0.73, 1.16	0.75	0.55, 1.04
	Trend			0.98	0.91, 1.05	0.93	0.84, 1.04
				$P = 0.54$		$P = 0.20$	
β -Cryptoxanthin, *μmol/L*	I	0.07	2718	1	Ref		
	II	0.11	2294	0.87	0.71, 1.07	0.91	0.62, 1.35
	III	0.16	2187	0.75	0.63, 0.89	0.83	0.63, 1.09
	IV	0.24	2191	0.81	0.68, 0.96	0.94	0.72, 1.25
	V	0.38	2089	0.74	0.61, 0.89	0.91	0.66, 1.26
	Trend			0.93	0.87, 0.99	1.01	0.93, 1.10
				$P = 0.03$		$P = 0.77$	
Vitamin A, *μmol/L*	I	1.33	2445	1	Ref		
	II	1.68	2285	0.91	0.76, 1.09	0.80	0.62, 1.03
	III	1.92	2392	0.91	0.76, 1.10	0.77	0.58, 1.01
	IV	2.20	2069	0.93	0.78, 1.11	0.79	0.62, 0.99
	V	2.69	2289	0.88	0.74, 1.04	0.79	0.60, 1.04
	Trend			0.97	0.92, 1.02	0.93	0.84, 1.03
				$P = 0.27$		$P = 0.17$	

(Continued)

TABLE 2 ***Continued***

Variable	Quintile[1]	Serum concentration[2]	Subjects, *n*	OR[3]	95% CI	OR[4]	95% CI
Vitamin C, *mmol/L*	I	8.52	2365	1	Ref		
	II	24.98	2238	0.90	0.75, 1.09	0.74	0.56, 0.98
	III	39.75	2357	0.71	0.60, 0.86	0.76	0.56, 1.04
	IV	52.24	2250	0.70	0.60, 0.81	0.61	0.47, 0.79
	V	70.41	2270	0.61	0.49, 0.74	0.50	0.36, 0.70
	Trend			0.82	0.76, 0.87	0.8	0.71, 0.89
				$P = 0.0001$		$P = 0.0001$	
Vitamin E, *μmol/L*	I	16.42	2305	1	Ref		
	II	20.06	2293	0.98	0.82, 1.19	0.89	0.61, 1.31
	III	23.45	2294	1.08	0.85, 1.37	1.15	0.80, 1.64
	IV	27.98	2292	1.09	0.88, 1.34	1.06	0.73, 1.52
	V	37.48	2296	0.91	0.74, 1.12	1.00	0.68, 1.48
	Trend			0.98	0.92, 1.05	1.03	0.99, 1.12
				$P = 0.61$		$P = 0.55$	
Bilirubin, *μmol/L*	I	6.84	4180	1	Ref		
	II	8.55	2202	0.79	0.67, 0.94	0.72	0.56, 0.93
	III	10.26	1679	0.82	0.68, 0.99	0.84	0.62, 1.13
	IV	11.97	1792	0.74	0.61, 0.91	0.84	0.61, 1.17
	V	17.1	1627	0.78	0.64, 0.93	0.81	0.61, 1.06
	Trend			0.89	0.83, 0.96	0.89	0.81, 0.98
				$P = 0.002$		$P = 0.018$	
TAOC, *μmol/L Trolox equivalents*	I	299.3	2296	1	Ref	1	Ref
	II	362.8	2296	1.08	0.90, 1.29	0.92	0.70, 1.21
	III	411.7	2296	0.92	0.76, 1.11	0.81	0.61, 1.08
	IV	464.4	2296	0.94	0.76, 1.15	0.92	0.68, 1.24
	V	545.0	2296	0.83	0.68, 1.03	0.70	0.50, 0.98
	Trend			0.93	0.87, 0.99	0.89	0.79, 1.00
				$P = 0.04$		$P = 0.05$	
Homocysteine, *μmol/L*	I	5.6	1073	1	Ref		
	II	7.2	1093	0.93	0.65, 1.34	0.86	0.52, 1.40
	III	8.6	1040	0.81	0.55, 1.19	0.61	0.34, 1.09
	IV	10.2	1038	0.97	0.68, 1.37	0.77	0.41, 1.45
	V	13.7	1055	0.95	0.70, 1.30	0.86	0.51, 1.45
	Trend			1.03	0.96, 1.09	0.96	0.84, 1.10
				$P = 0.37$		$P = 0.54$	

[1] Trend: OR for increase in serum concentration by 1 SD.
[2] Median.
[3] Adjusted for age, gender, race/ethnicity, cigarette smoking, OC/HRT use, diabetes, poverty-income ratio, and education and accounting for NHANES III sampling weights, stratification, and clustering (full model).
[4] Adjusted as for full model but restricted to never-smokers.

antioxidant species (32–35), we conducted a subanalysis restricted to never-smokers (36).

We found a strong and consistent inverse association between serum vitamin C concentrations and the prevalence of periodontitis. Nishida et al. (22) previously reported on the association between dietary vitamin C intake (not including supplements) and periodontitis prevalence in NHANES III. Interestingly, they found no association among never-smokers, and weak negative associations among former and current smokers. In contrast, our results show stronger inverse associations for serum vitamin C concentrations and periodontitis among never-smokers than in the full sample. This may reflect pharmacokinetic differences between smokers and nonsmokers; it may be the result of differential measurement error in the 24-dietary recall; or it may highlight consumption of vitamin C by ROS present in the circulation due to periodontal inflammation.

Mechanisms underpinning the apparently protective effects of vitamin C in maintaining tissue homeostasis include its key function in collagen synthesis and therefore maintenance of the structural integrity of the connective tissues as well as its role as a radical scavenger. Vitamin C has also been shown to antagonize C reactive protein-mediated increases in monocyte adhesion molecule expression and trans-endothelial migration (37) and to reduce neutrophilic polymorphonuclear leukocyte (PMNL) chemotaxis and phagocytosis in ascorbate deficient monkeys (38). Such vitamin C mediated mechanisms are independent of its radical scavenging activities and are likely to reduce the transit time of inflammatory/immune cells within the tissues and therefore potentially decrease the likelihood of tissue damage due to extracellular ROS release.

The results for Bilirubin are intriguing. It is formed as a bile pigment following the induction of the stress response protein heme oxygenase-1 in response to oxidative stress, inflammation, and other injuries (39). Heme oxygenase-1 catalyses the oxidative conversion of heme to biliverdin and bilirubin [by NAD(P)H-biliverdin reductase]. Bilirubin is generally regarded as a powerful antioxidant, with significant inverse relations between serum

TABLE 3 OR and 95% CI for prevalence of severe periodontitis by quintile of serum antioxidant concentration

Variable	Quintile[1]	Serum concentration[2]	Subjects, *n*	OR[3]	95% CI	OR[4]	95% CI
Lycopene, *μmol/L*	I	0.19	2451	1	Ref	1	Ref
	II	0.30	2192	0.92	0.70, 1.21	0.75	0.47, 1.21
	III	0.39	2425	1.13	0.87, 1.45	1.04	0.63, 1.70
	IV	0.52	2176	1.13	0.84, 1.52	1.02	0.56, 1.86
	V	0.71	2236	0.93	0.69, 1.26	1.07	0.64, 1.80
	Trend			1.03	0.94, 1.13	1.1	0.94, 1.28
				$P = 0.48$		$P = 0.23$	
α-Carotene, *μmol/L*	I	0.02	2708	1	Ref	1	Ref
	II	0.06	2845	0.91	0.70, 1.17	0.72	0.47, 1.11
	III	0.07	1750	0.94	0.70, 1.26	0.83	0.45, 1.55
	IV	0.09	2037	0.96	0.73, 1.26	0.91	0.49, 1.69
	V	0.17	2140	0.54	0.38, 0.77	0.61	0.32, 1.16
	Trend			0.85	0.67, 1.07	0.94	0.74, 1.18
				$P = 0.16$		$P = 0.57$	
β-Carotene, *μmol/L*	I	0.11	2358	1	Ref	1	Ref
	II	0.17	2265	1.06	0.82, 1.37	1.03	0.59, 1.82
	III	0.26	2462	1.00	0.75, 1.33	0.93	0.51, 1.68
	IV	0.41	2238	0.72	0.53, 0.99	0.87	0.50, 1.53
	V	0.73	2157	0.65	0.46, 0.93	0.83	0.51, 1.34
	Trend			0.77	0.66, 0.89	0.87	0.74, 1.02
				$P = 0.001$		$P = 0.09$	
Selenium, *nmol/L*	I	1.32	2396	1	Ref	1	Ref
	II	1.46	2185	1.07	0.83, 1.38	0.97	0.65, 1.45
	III	1.55	2352	1.12	0.88, 1.42	0.88	0.54, 1.42
	IV	1.66	2325	0.95	0.69, 1.31	1.13	0.68, 1.89
	V	1.83	2131	0.91	0.67, 1.22	0.81	0.48, 1.34
	Trend			0.97	0.89, 1.05	0.94	0.48, 1.34
				$P = 0.34$		$P = 0.30$	
Lutein, *μmol/L*	I	0.21	2647	1	Ref	1	Ref
	II	0.30	2078	0.98	0.77, 1.24	0.77	0.39, 1.51
	III	0.37	2312	0.96	0.76, 1.20	0.80	0.48, 1.33
	IV	0.47	2333	0.92	0.69, 1.24	0.87	0.54, 1.40
	V	0.69	2110	1.03	0.75, 1.41	1.02	0.58, 1.77
	Trend			1.02	0.93, 1.11	1.08	0.99, 1.16
				$P = 0.71$		$P = 0.07$	
Uric acid, *μmol/L*	I	208.2	2375	1	Ref	1	Ref
	II	267.7	2288	0.74	0.53, 1.03	0.61	0.33, 1.12
	III	309.3	2410	0.81	0.61, 1.08	0.95	0.56, 1.61
	IV	362.8	2194	0.75	0.56, 1.02	0.90	0.52, 1.55
	V	434.2	2213	0.69	0.49, 0.98	0.61	0.37, 1.02
	Trend			0.90	0.81, 1.00	0.86	0.73, 1.02
				$P = 0.064$		$P = 0.077$	
β -Cryptoxanthin, *μmol/L*	I	0.07	2718	1	Ref	1	Ref
	II	0.11	2294	0.96	0.78, 1.17	0.87	0.53, 1.43
	III	0.16	2187	0.66	0.51, 0.86	0.81	0.48, 1.35
	IV	0.24	2191	0.77	0.61, 0.98	0.85	0.57, 1.26
	V	0.38	2089	0.68	0.50, 0.93	0.83	0.51, 1.37
	Trend			0.92	0.81, 1.05	1.00	0.86, 1.15
				$P = 0.20$		$P = 0.94$	
Vitamin A, *μmol/L*	I	1.33	2445	1	Ref	1	Ref
	II	1.68	2285	0.85	0.63, 1.15	0.66	0.41, 1.07
	III	1.92	2392	0.83	0.63, 1.09	0.80	0.50, 1.23
	IV	2.20	2069	0.85	0.63, 1.14	0.69	0.42, 1.12
	V	2.69	2289	0.77	0.58, 1.03	0.69	0.43, 1.12
	Trend			0.92	0.85, 1.00	0.88	0.75, 1.00
				$P = 0.049$		$P = 0.14$	

(Continued)

TABLE 3 ***Continued***

Variable	Quintile[1]	Serum concentration[2]	Subjects, *n*	OR[3]	95% CI	OR[4]	95% CI
Vitamin C, *mmol/L*	I	8.52	2365	1	Ref	1	Ref
	II	24.98	2238	0.88	0.69, 1.13	0.67	0.41, 1.11
	III	39.75	2357	0.65	0.50, 0.85	0.63	0.40, 0.97
	IV	52.24	2250	0.58	0.44, 0.76	0.47	0.29, 0.75
	V	70.41	2270	0.53	0.42, 0.68	0.38	0.26, 0.63
	Trend			0.76	0.69, 0.84	0.71	0.58, 0.86
				$P = 0.0001$		$P = 0.001$	
Vitamin E, μ*mol/L*	I	16.42	2305	1	Ref	1	Ref
	II	20.06	2293	0.91	0.70, 1.18	0.90	0.55, 1.47
	III	23.45	2294	1.22	0.88, 1.71	1.39	0.89, 2.18
	IV	27.98	2292	1.13	0.82, 1.56	1.27	0.79, 2.10
	V	37.48	2296	1.01	0.75, 1.36	0.89	0.56, 1.43
	Trend			0.97	0.90, 1.05	0.92	0.81, 1.05
				$P = 0.43$		$P = 0.23$	
Bilirubin, μ*mol/L*	I	6.84	4180	1	Ref	1	Ref
	II	8.55	2202	0.75	0.61, 0.93	0.85	0.55, 1.31
	III	10.26	1679	0.69	0.53, 0.90	0.67	0.39, 1.18
	IV	11.97	1792	0.65	0.49, 0.85	0.55	0.35, 0.87
	V	17.10	1627	0.65	0.49, 0.93	0.98	0.60, 1.60
	Trend			0.85	0.74, 0.98	0.87	0.72, 1.06
				$P = 0.023$		$P = 0.16$	
TAOC, μ*mol/L Trolox equivalents*	I	299.3	2296	1	Ref	1	Ref
	II	362.8	2296	0.89	0.62, 1.16	0.84	0.48, 1.47
	III	411.7	2296	0.67	0.48, 0.93	0.80	0.47, 1.35
	IV	464.4	2296	0.77	0.57, 1.04	0.95	0.58, 1.55
	V	545.0	2296	0.63	0.47, 0.85	0.55	0.33, 0.93
	Trend			0.85	0.77, 0.94	0.79	0.67, 0.94
				$P = 0.001$		$P = 0.009$	
Homocysteine, μ*mol/L*	I	5.6	1073	1	Ref	1	Ref
	II	7.2	1093	1.90	1.13, 3.21	1.44	0.73, 2.83
	III	8.6	1040	1.25	0.70, 2.23	0.66	0.35, 1.25
	IV	10.2	1038	1.38	0.79, 2.43	0.95	0.42, 2.16
	V	13.7	1055	1.39	0.88, 2.19	0.68	0.32, 1.43
	Trend			1.06	0.97, 1.17	0.93	0.73, 1.18
				$P = 0.20$		$P = 0.52$	

[1] Trend: OR for increase in serum concentration by 1 SD.
[2] Median.
[3] Adjusted for age, gender, race/ethnicity, cigarette smoking, OC/HRT use, diabetes, poverty-income ratio, and education and accounting for NHANES III sampling weights, stratification, and clustering (full model).
[4] Adjusted as for full model but restricted to never-smokers.

levels demonstrated in atherosclerosis and coronary artery disease (39). Biliverdin has also been shown in rat models to protect against lipopolysaccharide-mediated lung damage by increasing circulating interleukin (IL)-10 levels and lowering proinflammatory cytokine (e.g., IL-6) levels. These reports are consistent with the inverse association of serum bilirubin with the prevalence of periodontitis in the presen t study and may reflect inhibition of common proinflammatory pathways.

One limitation to our study is that residual confounding may, at least in part, explain some inverse associations. Multivariate adjustment markedly attenuated most of the inverse associations indicating the presence of substantial confounding. Furthermore, the inverse associations seen in the full model with carotenoids (α-carotene, β-carotene, β-cryptoxanthin) were not evident among never-smokers. Given that carotenoid concentrations will depend in part upon dietary intake, and that smokers have reduced dietary antioxidant intakes (40), other relevant health behaviors (such as fruit and vegetable consumption) may introduce confounding in the analyses of carotenoids. However, given its strength and consistency, the association for vitamin C is not likely to be entirely due to confounding. Furthermore, low vitamin C intake has been implicated as a significant factor for total tooth loss (41), and edentulous patients were shown to have lower serum vitamin C concentrations than their dentate counterparts (42).

Data from small cross-sectional studies has demonstrated equivocally reduced plasma TAOC in periodontitis patients relative to age/sex-matched controls (12,43). The current analysis is based on a large population survey and provides, to our knowledge, the first strong evidence for inverse associations between serum antioxidant concentrations and periodontitis prevalence. Low serum antioxidant concentrations could be the result of periodontal inflammation or could be a risk factor for periodontitis, or indeed both, and the results of the present cross-sectional study are consistent with all of the above explanations.

Chapple et al. (43) have demonstrated that some of the reduction in plasma TAOC in periodontitis arises secondarily to the oxidative stress induced by periodontal inflammation. Taken together, these findings may have significant implications for periodontitis as a risk factor for diseases such as stroke, cardiovascular disease, and type-2 diabetes, which have low-grade systemic inflammation implicated in their pathogenesis (44). Longitudinal studies are needed to ascertain whether successful periodontal therapy reduces both the oxidative and nonoxidative inflammatory burden within the peripheral vasculature and also whether serum antioxidant concentrations are true risk factors for periodontitis. If confirmed, intervention studies involving antioxidant approaches would be indicated to determine the potential for reducing the risk of periodontitis.

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