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G.D. Slade[1]*, S. Offenbacher[2], J.D. Beck[1], G. Heiss[3], and J.S. Pankow[3]

[1]Department of Dental Ecology, [2]Department of Periodontology, and [3]Department of Epidemiology, University of North Carolina at Chapel Hill, CB#7450, Chapel Hill, NC 27599-7450, USA; *corresponding author, gary_slade@dentistry.unc.edu

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ABSTRACT

Moderate elevation of serum C-reactive protein (CRP) is a risk factor for cardiovascular disease among apparently healthy individuals, although factors that create this inflammatory response in the absence of systemic illness have not been clarified. This study aimed to: (1) evaluate associations among periodontal disease, established risk factors for elevated CRP, and CRP levels within the US population; and (2) determine whether total tooth loss is associated with reduced CRP. Data were obtained from the third National Health and Nutrition Examination Survey. A random sample of the US population was interviewed in their homes and examined at mobile examination centers. CRP was quantified from peripheral blood samples and analyzed as a continuous variable and as the prevalence of elevated CRP ($\geq$ 10 mg/L). Some 12,949 people aged 18+ years who had periodontal examinations and an additional 1817 edentulous people aged 18+ years were included in the analysis. Dentate people with extensive periodontal disease (> 10% of sites with periodontal pockets 4+ mm) had an increase of approximately one-third in mean CRP and a doubling in prevalence of elevated CRP compared with periodontally healthy people. Raised CRP levels among people with extensive periodontal disease persisted in multivariate analyses ($P < 0.01$), with established risk factors for elevated CRP (diabetes, arthritis, emphysema, smoking, and anti-inflammatory medications) and sociodemographic factors controlled for. However, CRP levels were similarly raised in edentulous people. Furthermore, the established risk factors for elevated CRP modified relationships between oral status and CRP levels. Periodontal disease and edentulism were associated with systemic inflammatory response in the US population, most notably among people who had no established risk factors for elevated CRP.

KEY WORDS: epidemiology, inflammatory mediators, periodontics, molecular biology, inflammation.

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INTRODUCTION

C-reactive protein (CRP) is an acute-phase reactant produced by the liver in response to diverse inflammatory stimuli, including heat, trauma, infection, and hypoxia (Pepys and Baltz, 1983). In patients with overwhelming systemic infection, serum levels of CRP can exceed 100 mg/L, providing a useful marker for tracking the course of the infection. However, the clinical relevance of much smaller increases in CRP has been highlighted recently in epidemiological studies demonstrating that individuals with "high-normal" values of CRP have increased risks for chronic diseases that have an inflammatory basis, including cardiovascular disease. For example, the longitudinal Physicians' Health Study, which examined an initially healthy population, found that a relatively modest increase in CRP (*i.e.*, > 2.11 mg/L, corresponding to the upper quartile of the distribution in that study) was a risk factor for myocardial infarction and stroke (Ridker *et al.*, 1997).

Established risk factors for "high-normal" values of CRP within the general population include older age, cigarette smoking, chronic bacterial infections, and chronic bronchial inflammation (Palosuo *et al.*, 1986; Saikku *et al.*, 1992; Patel *et al.*, 1995; Mendall *et al.*, 1996; Ridker *et al.*, 1997). However, raised CRP levels have been observed among individuals with no apparent established risk factors for elevated CRP, suggesting that other pathological conditions may constitute an additional stimulus for a systemic inflammatory response among some individuals.

Periodontal disease is a chronic inflammatory process that occurs in response to a predominantly Gram-negative bacterial infection originating from dental plaque. Clinical manifestations include gingival inflammation, formation of periodontal pockets between the gingiva and tooth roots that promote the overgrowth of anaerobic bacteria, and subsequent ulceration of the epithelium and destruction of collagen, periodontal ligament, and bone that forms the attachment between the jaw and tooth root. While the etiological role of bacteria has been firmly established *in vitro* and *in vivo*, it is only recently that researchers have begun to identify local and systemic inflammatory processes that encourage a pathological response to an initial, commensal microflora (Page, 1995; Offenbacher, 1996). For example, impaired systemic host defense mechanisms among smokers have been cited as the probable mechanism responsible for their elevated rates of periodontal disease compared with non-smokers (Barbour *et al.*, 1997). Equally compelling is the evidence from experimental studies demonstrating enhanced release of inflammatory mediators (for example, PGE_2, IL-1β, TNFα) from peripheral monocytes drawn from patients with periodontal disease when those monocytes are challenged, *in vitro*, with bacterial lipopolysaccharide (Shapira *et al.*, 1994; Salvi *et al.*, 1997).

The tissue destruction caused by periodontal infection can be substantial. Patients with extensive periodontitis can have deep periodontal pockets around many or all of their teeth, the aggregated epithelial lesions being equivalent in size to an ulcerated wound as large as 50 cm^2, according to

clinical estimates. However, the disease typically remains asymptomatic for decades, during which time it can be detected only by clinical examination with a periodontal probe or with intra-oral radiographs. Therefore, severe periodontal disease, which occurs in approximately 14% of the US adult population (National Institute of Dental Research, 1987), is rarely considered in the medical assessment of patients' systemic health status. Consequently, if a relationship exists between periodontal disease and systemic CRP within the population at large, it has the potential for substantial clinical relevance in helping to explain circumstances in which an intra-oral source of infection can create a systemic inflammatory response, therefore placing "apparently healthy" patients at increased risk of cardiovascular disease. Such an association could also represent a mechanism underlying recent epidemiological findings that oral diseases appear to be risk factors for cardiovascular disease (Beck *et al.*, 1996).

The purpose of this study was to investigate the effects of established risk factors for elevated CRP and selected oral conditions on CRP levels within the US population. We aimed first to compare levels of CRP among subgroups defined by periodontal disease and systemic health status. We hypothesized that, after established risk factors were controlled for, CRP levels would be higher among people with more extensive periodontal disease. Second, we aimed to evaluate if total tooth loss was associated with reduced CRP levels. We hypothesized that CRP levels would be lower among edentulous people compared with dentate people who had extensive periodontal disease, after established risk factors for elevated CRP were controlled for.

MATERIALS & METHODS

Data on CD-ROM were obtained from the third National Health and Nutrition Examination Survey (NHANES III), a cross-sectional study, conducted between 1988 and 1994, of the United States population aged two months and older. Full documentation of the survey has been provided elsewhere (DHHS, 1996), and descriptive findings on oral health status from the first phase have been reported (Kleinman and Drury, 1996). In summary, the design of NHANES III was a complex, multi-stage, stratified, clustered sample survey of the US civilian, non-institutionalized population. Interviews were conducted in respondents' homes, standardized examinations that included dental examinations were conducted at mobile examination centers, and analyses of most biological samples were conducted by contracting laboratories. The analyses reported here were limited to people aged 18+ years who had a dental examination and for whom CRP data were available. Younger subjects were excluded, in an attempt to reduce counting of false periodontal pockets which occur frequently around erupting teeth.

CRP measurements were made from fasting peripheral blood samples collected by venipuncture. CRP was quantified by latex-enhanced nephelometry, for which the minimum detectable concentration of CRP was 3.0 mg/L (Gunter *et al.*, 1996). Quality control was monitored with reference to standard preparations and by the regular conduct of replicate assays of bench controls. Repeat testing was done to verify all samples with concentrations exceeding 100 mg/L. The periodontal examination included measurement of probing pocket depth according to the National Institute of Dental and Craniofacial Research protocol (National Institute of Dental Research, 1987). Measurements were made in two randomly-selected quadrants of the mouth for all teeth other than third molars, partially erupted teeth, or retained roots. Two sites were measured for each tooth: mesio-facial and mid-facial. Six calibrated dentists conducted the periodontal examinations, and their levels of inter-examiner reliability were found to be acceptable (Kingman *et al.*, 1998).

The dependent variable for analyses was serum CRP level, which was used both as a continuous variable and as a dichotomous variable (< 10 mg/L *vs.* ≥ 10 mg/L). This dichotomy has been used as evidence of clinically meaningful infection (Tracy *et al.*, 1997) and is described below as "elevated CRP". When used as a continuous variable, values below 3.0 mg/L were imputed to 1.5 mg/dL—halfway between zero and the threshold of detection. For linear regression analysis, the natural log transformation of CRP values was used as the dependent variable, to reduce the highly skewed distribution of the observed CRP values.

Effects of periodontal disease were evaluated among dentate persons by comparison of subjects' CRP levels with their extent of periodontal pocketing at the 4+ mm threshold. Extent scores (Carlos *et al.*, 1986) represent the percentage of probed sites that have pocketing of at least four millimeters, and this was categorized into three levels (0%, 1 to 10%, and > 10% of sites) to provide an ordinal indicator of exposure to periodontal infection. For this analysis, pocket depth was selected as the exposure variable describing periodontal disease, since it was thought to provide a better proxy indicator for existing periodontal infection than other markers of periodontal disease, such as attachment loss or recession, which reflect current and historical disease activity.

Stratified and multivariate analyses were undertaken with additional covariates that were selected from the large number of sociodemographic and health-status measures available in the NHANES III study. Those variables were selected if they met any of the following criteria:

(1) There was evidence from previous studies that the variable was an established risk factor for both elevated CRP and periodontal disease. Variables meeting this criterion were cigarette smoking (measured in pack-years) and serum glycosylated hemoglobin (measured as percentage), which served as a marker of average glycemia and diabetic control. This criterion was necessary to establish whether any periodontal-CRP association could be attributed to a common antecedent that caused both periodontal disease and elevated CRP.

(2) There was evidence from previous studies or theoretical grounds to believe that the variable was a risk factor for elevated CRP and was associated (although perhaps not causally) with periodontal disease. Variables meeting this criterion were: the number of non-steroidal anti-inflammatory drugs reportedly taken during the previous month and reported histories of arthritis, chronic bronchitis, and emphysema.

(3) Basic sociodemographic characteristics. Variables meeting this criterion were: age, sex, race/ethnicity, and socio-economic status (SES), measured as the ratio of household income to the poverty level.

To evaluate our first hypothesis, we examined the periodontal-CRP association among strata defined by these covariates to find evidence of confounding or modification of the association. Then, periodontal

disease and covariates were evaluated collectively in a linear regression model in which the outcome variable was the natural logarithm of CRP. First-order explanatory variables were introduced into the model, and those that were statistically significant ($P < 0.05$) were retained. Then, two-way interactions between periodontal disease and all the remaining independent variables were evaluated and retained if statistically significant ($P < 0.05$). Survey phase (1988-91 or 1991-94) and dental examiner (coded as examiner 1 through examiner 6) were included as additional explanatory variables to control for variations that were observed in periodontal disease measurement among dental examiners and between NHANES III phases (Slade and Beck, 1999). This modeling strategy was replicated by means of logistic regression in which elevated CRP ($\geq$ 10 mg/L) was the dependent variable.

To evaluate our second hypothesis, we first compared CRP levels between dentate and edentulous people. Then, based on findings from the preceding analysis of dentate people, we categorized all subjects according to the presence or absence of at least one established risk factor for elevated CRP and compared CRP levels among groups defined by combinations of established risk factors and oral disease.

Direct age-standardized estimates were calculated with the 1980 US population as the standard. All analysis were conducted in SUDAAN v7.5 using the design and weight options specified in the NHANES III documentation (DHHS, 1996). Hence, results from this study can be generalized to the US population aged 18+ years.

RESULTS

Some 39,695 persons were selected for the two phases of NHANES III of whom 33,994 (86%) were interviewed in their homes. Seventy-eight percent (30,818) of the selected persons attended the mobile examination center, and 28,059 of them had dental examinations. Excluded from periodontal assessments were 8786 subjects who were aged less than 12 years, 1957 who were edentulous, 1165 who had medical contraindications, and 254 who had no periodontal assessment for other (unspecified) reasons. The first aim of this study was limited to 12,949 dentate people aged 18+ years who had both periodontal and CRP data, while the second aim included an additional 1817 people aged 18+ years who were edentulous.

Among dentate and edentulous people, the distribution of CRP levels was highly skewed, being undetectable (< 3.0 mg/L) for 72.0% of people (95% CI = 69.6-74.4%) and increasing to a maximum of 252 mg/L. Some 7.3% of people (95% CI = 6.5-8.1%) had elevated CRP ($\geq$ 10 mg/L). The prevalence of edentulism was 9.6% (95% CI = 8.6-10.6%), and, among dentate people, the prevalence of extensive periodontal pocketing (> 10% of sites having pockets of 4+ mm) was 7.8% (95% CI = 6.4-9.2%). However, three-quarters of dentate people had no periodontal pockets of 4+ mm.

Bivariate Associations between Periodontal Disease and CRP among Dentate People

There was an approximate two-fold difference in mean CRP levels between the youngest age group (18-24 years, mean = 2.7 mg/L) and the oldest age group (75+ years, mean = 4.9 mg/L). Hence, all other bivariate associations were assessed based on age-standardized data. Among dentate persons aged 18+ years, the age-standardized mean CRP level was one-third higher in the group with most extensive periodontal pockets (> 10% of sites) compared with that in the group having no pockets, and there was a two-fold difference in prevalence of elevated CRP (Table 1—all persons). The mean and prevalence values for the group with intermediate extent of periodontal pockets (from 1 to 10% of sites) were very similar to those in the group with no pockets.

In stratified analysis, the association between age-standardized CRP levels and extent of periodontal pockets generally persisted, although the magnitude of the association varied among strata (Table 1). For example, there were larger differences in CRP levels between periodontal pocket groups in males (four-fold difference in prevalence) compared with females (two-thirds difference in prevalence). However, higher CRP levels were observed among groups with no periodontal pockets or intermediate pocketing within some strata. For example, among blacks, the mean CRP level was greatest for people with no periodontal pockets. For most established risk factors for elevated CRP, the periodontal-CRP association appeared weakest for the subgroups with the risk factor and strongest for the subgroups without the risk factor. For example, among people with poor diabetic control (glycosylated hemoglobin > 6.5%), there was no clear association between periodontal pockets and CRP, and there was an inverse periodontal-CRP association among people with a history of chronic bronchitis. In contrast, CRP levels were clearly raised in the presence of extensive periodontal pocketing for people without those conditions.

Multivariate Associations among Periodontal Disease, Established Risk Factors for Elevated CRP, and CRP among Dentate People

Extent of periodontal pockets persisted as an independent, statistically significant explanatory variable in the linear regression model that controlled for 11 other variables (Table 2). The parameter estimate (β) for > 10% pocket depth extent was 0.14, indicating an increase of 0.14 in mean log CRP levels for the group with the most extensive periodontal disease (> 10% extent of pocketing) compared with the reference group (no pocketing). However, the parameter estimate for the 1 to 10% group was close to zero, indicating virtually no increase for the group with intermediate periodontal disease. These results are consistent with the apparent threshold effect of periodontal disease observed in the age-standardized findings (Table 1). The parameter estimate of 0.14 for the group with most extensive periodontal disease was midway between the estimates for bronchitis and arthritis, indicating that the effect of severe pocketing on CRP levels was of a magnitude comparable with that of those two conditions. Of the variables examined in the stratified analysis, emphysema was the only one that did not reach statistical significance in this multivariate model. Interactions between periodontal pocketing and established risk factors for elevated CRP were not statistically significant ($P > 0.05$), indicating that the effect of periodontal disease was not conditional upon any of those individual risk factors.

Results from the logistic regression model, in which the outcome was presence of elevated CRP ($\geq$ 10 mg/L), generally confirmed the associations observed in Table 2. The approximate two-fold increase in odds of elevated CRP associated with extensive periodontal pocketing was comparable, in magnitude, with the effects of chronic bronchitis (odds ratio = 1.83) and > 10 pack-years of cigarette exposure

(odds ratio = 1.55, Table 3). However, there was no increase in odds for people with moderate periodontal pocketing (odds ratio = 0.98 relative to people with no pocketing). The effect of extensive periodontal pocketing was similar, in magnitude, to the effects observed when only age was adjusted for. That is, the greater age-adjusted prevalence of CRP ≥ 10 mg/L for people with extensive pocketing, as reported in Table 1, was equivalent to an odds ratio of 2.24 relative to people with no pocketing (data not reported). This was only marginally greater than the multivariate-adjusted odds ratio of 1.83 observed in Table 3.

For further investigation of the observed threshold effect of periodontal disease, additional modelling was done with different cut-points of periodontal pocket extent scores. In a linear regression model that controlled for the same variables as in Table 2, parameter estimates were 0.02 ($P > 0.05$) for 1 to 5% extent and 0.08 ($P < 0.01$) for > 5% extent compared with a reference category of 0% extent. In a second model, the linear regression parameter estimates were 0.04 ($P = 0.03$) for 1 to 15% extent and 0.13 ($P < 0.01$) for > 15% extent. In a third model that used extent score as a continuous variable together with extent squared, the continuous variable was significant ($P < 0.01$), but the squared term was not statistically significant ($P = 0.89$). Hence, this additional modeling suggested that risk of CRP elevation was fairly constant for periodontal extent scores between zero and 5%, increased through extent scores of 10%, then leveled off at higher extent scores.

Table 1. Age-standardized C-reactive Protein (CRP) Levels among Periodontal Disease Subgroups Aged 18+ Years

Stratum		% of Sites with Periodontal Pocketing 4+ mm	Unweighted n	Mean (SE) CRP (mg/L)	% (SE) of Persons with ≥ 10 mg/L CRP
All persons		0%	9146	3.3 (0.1)	6.0 (0.4)
		1-10%	2253	3.4 (0.2)	5.5 (0.7)
		> 10%	1550	4.5 (0.3)[b]	12.5 (2.3)[b]
Sex	Male	0%	3994	2.6 (0.1)	2.9 (0.4)
		1-10%	1191	3.1 (0.2)	4.3 (0.8)
		> 10%	948	4.1 (0.5)[b]	10.5 (3.1)[a]
	Female	0%	5152	3.8 (0.1)	8.6 (0.6)
		1-10%	1062	4.1 (0.4)	7.2 (1.2)
		> 10%	602	4.8 (0.4)[b]	14.4 (2.3)[a]
Race/ethnicity	White	0%	3804	3.2 (0.1)	5.4 (0.4)
		1-10%	617	3.2 (0.3)	4.6 (0.8)
		> 10%	362	4.1 (0.5)[a]	12.2 (3.9)
	Black	0%	2245	4.5 (0.2)	10.0 (0.7)
		1-10%	779	4.1 (0.3)	8.5 (1.3)
		> 10%	640	5.3 (0.4)	14.6 (2.0)[a]
	Hispanic	0%	2680	4.0 (0.3)	6.9 (1.0)
		1-10%	781	4.0 (0.3)	8.2 (1.4)
		> 10%	498	4.1 (0.3)	7.3 (1.0)
	Other	0%	417	3.1 (0.3)	7.0 (2.0)
		1-10%	76	3.7 (1.4)	2.5 (2.0)
		> 10%	50	4.9 (1.3)	12.6 (5.1)
Household income:poverty ratio	≤ 1.0	0%	1774	4.1 (0.3)	7.5 (0.9)
		1-10%	575	4.0 (0.3)	6.5 (1.2)
		> 10%	444	5.6 (0.7)[a]	19.0 (4.7)[a]
	1.0-< 2.0	0%	2153	3.9 (0.2)	8.5 (1.0)
		1-10%	578	3.2 (0.3)	5.6 (1.4)
		> 10%	442	4.9 (0.6)	12.0 (2.7)
	2.0-< 3.0	0%	1587	3.1 (0.2)	4.9 (0.7)
		1-10%	364	3.7 (0.5)	5.6 (1.3)
		> 10%	244	3.4 (0.2)	6.6 (1.8)
	≥ 3.0	0%	2874	3.0 (0.1)	5.5 (0.6)
		1-10%	522	3.2 (0.3)	5.3 (1.1)
		> 10%	270	2.9 (0.2)	5.3 (1.4)
Pack-years of cigarettes	None	0%	5123	3.1 (0.1)	5.4 (0.5)
		1-10%	1100	3.1 (0.2)	4.5 (0.8)
		> 10%	606	4.8 (0.6)[b]	13.9 (2.5)[b]
	> 0-10	0%	2001	3.2 (0.1)	5.5 (0.8)
		1-10%	506	3.0 (0.4)	3.8 (1.3)
		> 10%	336	4.4 (0.6)	11.6 (4.0)
	> 10	0%	1827	3.5 (0.3)	6.9 (1.0)
		1-10%	598	3.7 (0.4)	5.8 (1.2)
		> 10%	574	4.6 (0.5)[a]	11.5 (3.0)

Association between Total Tooth Loss and CRP

The age-standardized mean CRP level for edentulous people was 4.2 mg/L (95% CI = 3.8-4.6 mg/L) and their age-standardized prevalence of elevated CRP (≥ 10 mg/L) was 10.4% (95% CI = 8.3-12.5%). These values were not significantly different ($P > 0.35$) from those observed for dentate people with extensive periodontal pockets but were significantly greater ($P \leq 0.01$) than the values observed for dentate people with no pockets and dentate people whose extent scores were between zero and 10%.

Additional analysis indicated that most edentulous people had at least one of the established risk factors for elevated CRP levels observed in the analysis of dentate people (Table 2). For example, 91.2% of edentulous persons (95% CI = 90.2-92.1%) had at least one of the following five risk factors: glycosylated hemoglobin ≥ 5.7%, a reported history of arthritis, a reported history of bronchitis, being a current or former smoker, or taking > 25 NSAIDs in the previous month. In contrast, 66.0% of dentate people (95% CI = 64.2-67.8%) had one or more of those conditions.

When the combined effects of oral status and those five risk

Table 1 *(continued)*

Stratum		% of Sites with Periodontal Pocketing 4+ mm	Unweighted n	Mean (SE) CRP (mg/L)	% (SE) of Persons with ≥ 10 mg/L CRP
Glycosylated hemoglobin	≤ 5.7%	0%	7395	3.1 (0.1)	5.0 (0.4)
		1-10%	1764	3.1 (0.2)	4.7 (0.7)
		> 10%	1053	4.1 (0.4)[b]	10.8 (2.2)[b]
	5.8-6.5%	0%	1211	4.7 (0.4)	13.9 (3.0)
		1-10%	340	4.6 (0.6)	7.1 (1.7)
		> 10%	316	5.2 (0.3)	15.1 (2.8)
	> 6.5%	0%	494	7.4 (1.3)	26.1 (6.5)
		1-10%	134	7.8 (1.4)	16.7 (6.3)
		> 10%	173	7.4 (0.8)	22.0 (4.2)
Arthritis history	No	0%	7652	3.2 (0.1)	5.5 (0.4)
		1-10%	1906	3.5 (0.2)	5.5 (0.7)
		> 10%	1296	4.2 (0.3)[b]	11.4 (2.2)[b]
	Yes	0%	1493	4.2 (0.5)	14.1 (5.1)
		1-10%	347	3.8 (0.4)	6.8 (1.5)
		> 10%	253	5.6 (0.6)	15.2 (3.1)
Chronic bronchitis history	No	0%	8677	3.2 (0.1)	5.4 (0.4)
		1-10%	2180	3.4 (0.2)	5.2 (0.7)
		> 10%	1486	4.5 (0.4)[b]	12.9 (2.4)[b]
	Yes	0%	468	5.1 (0.6)	14.8 (2.9)
		1-10%	73	4.4 (0.9)	7.9 (3.0)
		> 10%	64	4.4 (0.7)	4.7 (1.8)[b]
Emphysema history	No	0%	9041	3.2 (0.1)	5.9 (0.4)
		1-10%	2231	3.4 (0.2)	5.4 (0.7)
		> 10%	1526	4.5 (0.3)[b]	12.6 (2.3)[b]
	Yes	0%	103	5.4 (1.3)	10.8 (4.5)
		1-10%	22	6.2 (0.8)	12.0 (2.8)
		> 10%	24	3.9 (0.6)	11.5 (4.5)
No. of NSAIDs in last month	None	0%	2816	3.2 (0.1)	5.4 (0.7)
		1-10%	795	3.1 (0.2)	4.9 (0.8)
		> 10%	628	4.7 (0.6)[b]	14.6 (4.4)[a]
	1-25	0%	5232	3.2 (0.1)	5.6 (0.5)
		1-10%	1226	3.8 (0.4)	6.5 (1.1)
		> 10%	738	4.1 (0.5)	9.5 (2.0)
	> 25	0%	1064	4.0 (0.4)	8.8 (1.4)
		1-10%	223	3.2 (0.3)	4.1 (1.2)[b]
		> 10%	182	4.1 (0.4)	11.0 (2.3)

[a] $0.01 < P < 0.05$.
[b] $P < 0.01$.

factors were evaluated, edentulous people continued to have high age-standardized mean CRP values that were similar to those of people with extensive periodontal pocketing (Fig.). However, the analysis also revealed that the relationship between oral status and CRP was conditional upon the presence or absence of established risk factors for elevated CRP. That is, the difference in CRP levels between people who were periodontally healthy (dentate people with 0% or 1 to 10% pockets) and people who were not (> 10% pockets or edentulous) was greater in the absence of established risk factors than in the presence of established risk factors. Stated another way, established risk factors were associated with significantly raised CRP levels ($P < 0.05$) only among the two periodontally healthy subgroups. A similar phenomenon was observed when the outcome variable was prevalence of elevated CRP. The findings from the Figure were further supported in a linear regression model which indicated a statistically significant ($P < 0.01$) interaction between oral status and the presence or absence of the five established risk factors. That model, which used log CRP as the dependent variable, also controlled for age, sex, race, and income:poverty ratio (data not shown).

DISCUSSION

This study has identified edentulism and periodontal disease as two oral conditions associated with an increased systemic inflammatory response within the US population. The association persisted after we controlled for established risk factors for elevated CRP, and, in the case of periodontal disease, the magnitude of the association was comparable with that identified for conditions such as chronic bronchitis and cigarette smoking (Tables 2, 3). Furthermore, these established risk factors modified the association between oral status and CRP levels (Fig.). That is, extensive periodontal pockets and edentulism had a stronger association with CRP levels among people with no established risk factors compared with people who had one or more established risk factors. The stronger effect of oral status among the subgroup with no established risk factors probably reflects the absence of other contributing causes of an acute-phase response, and in many respects this subgroup provides a more controlled test of the potential for oral conditions to elicit an acute-phase response. This modifying effect may further explain why some previous studies examining established risk factors for CRP found raised CRP levels even among "apparently healthy" people (Ridker *et al.*, 1997).

These results confirm those of previous cross-sectional studies of periodontal-CRP associations conducted among selected clinical samples (Ueta *et al.*, 1993; Ebersole *et al.*, 1997; Meurman *et al.*, 1997). In addition, diabetes, cigarette smoking, diabetes, arthritis, and bronchitis were confirmed as correlates of elevated CRP. The major strength of this study from a public health perspective is its ability to generalize these associations to the US population. Whereas previous studies of selected clinical samples have demonstrated systemic

Table 2. Linear Regression Analysis of Log-transformed Mean C-reactive Protein

Independent Variable[a]	df	F[b]	P	Parameter	β (SE)
Sex (ref = Male)	1	98.2	< 0.01	Female	0.24 (0.02)
Race/ethnicity (ref = White)	3	7.3	< 0.01	NH black	0.12 (0.03)
				Mex-Am	0.08 (0.03)
				Other	-0.02 (0.04)
Income:poverty ratio	3	5.5	< 0.01	≤ 1.0	0.10 (0.03)
(ref = > 3.0)				1.0-< 2.0	0.10 (0.03)
				2.0-< 3.0	0.04 (0.02)
Pack-years of cigarettes	2	7.6	< 0.01	> 10	0.08 (0.02)
(ref = None)				1-10	0.01 (0.02)
Glycosylated hemoglobin	2	56.8	< 0.01	> 6.5%	0.49 (0.07)
(ref = < 5.7%)				5.7-6.5%	0.29 (0.04)
Arthritis history (ref = No)	1	7.0	0.01	Yes	0.09 (0.03)
Chronic bronchitis history (ref = No)	1	9.2	< 0.01	Yes	0.18 (0.06)
No. of NSAIDs (ref = None)	2	5.6	< 0.01	> 25/month	0.08 (0.03)
				1-25/month	0.00 (0.02)
Pocket depth extent (Ref = 0%)	2	5.2	< 0.01	> 10%	0.14 (0.04)
				1-10%	0.01 (0.03)
Intercept					0.82 (0.08)

[a] Additional independent variables included in this model were: age (7 categories), NHANES III examination phase (2 categories), and dental examiner (6 categories), all of which were statistically significant ($P < 0.01$)

[b] For all terms in model, $F_{29,11452} = 63.0$, $P < 0.01$, $R^2 = 0.097$.

inflammatory responses to periodontal disease, the current findings demonstrate the same response within the US population. The large sample size and broad scope of variables available for analysis in this study are additional strengths, permitting periodontal-CRP associations to be estimated with good statistical precision, even after stratification for other competing determinants of CRP, such as chronic bronchitis, which themselves have relatively low prevalence. A novel finding was that oral conditions had their strongest association with CRP levels in population subgroups that did not have systemic diseases (Table 1).

The cross-sectional design of NHANES III constitutes the major weakness of this study for the purpose of drawing causal inferences. Specifically, the lack of temporal association in this study means that it is not possible to determine if one factor (periodontal disease or elevated CRP) preceded the other, a long-established requirement for making causal inferences in observational epidemiology (Kleinbaum *et al.*, 1982). Consequently, the associations reported in this study cannot be used to infer that periodontal pocketing is a risk factor for elevated systemic CRP levels. Furthermore, despite the large sample size and number of variables studied, it remains possible that other unmeasured characteristics, such as liver function or genetic predisposition, could confound the associations observed here.

These findings demonstrate that there is a threshold, rather than a monotonic pattern, in the relationship between extent of periodontal pockets and systemic CRP levels. For an individual who had a full complement of natural teeth and who was examined in general dental practice by means of the periodontal screening and recording protocol advocated by the American Academy of Periodontology (Nasi, 1994), the threshold of 10% used in this study would correspond to the presence of at least three teeth with periodontal pockets of 4+ mm. This threshold of periodontal disease was observed for 7.8% of the dentate US population. The presence of a threshold, rather than linear, relationship among the three levels of pocketing and CRP may be a consequence of the relatively crude nature of periodontal pocket measurements, which represents only a proxy measure for periodontal infection. For example, individuals with only one or two periodontal pockets of 4+ mm may be less likely to have active infection at those sites. Analysis of the periodontal microflora or local measures of inflammation within the periodontal pocket may reveal stronger patterns of association with systemic CRP. While some periodontal pathogens were quantified in NHANES III, those data are not yet available in the public-release dataset.

The most surprising finding from this study concerns the elevation of CRP among edentulous people. The finding that CRP levels in edentulous people were roughly equivalent to those in the dentate group with extensive periodontal pockets refuted our prior hypothesis that edentulous people, who necessarily have no periodontal infection, would have CRP levels that were similar to those of periodontally healthy individuals. Viewed another way, the results in the Fig. indicate that retention of periodontally diseased teeth is associated with no greater increase in CRP than the extraction of all teeth. Periodontal disease typically accounts for up to one-half of tooth extractions in studies of adult dental patients in the US (Phipps and Stevens, 1995), and hence it is likely that many edentulous persons had a history of severe periodontal disease. However, it is unlikely that an acute-phase reactant such as CRP would remain elevated if the source of that elevation had been periodontal infection that occurred earlier in the lifetime of these edentulous persons.

It remains possible that additional local or systemic inflammatory diseases or risk factors, other than those examined here, could account for raised CRP levels observed among edentulous people. For example, although not reported above, 56% of edentulous people had one or more oral mucosal lesions, compared with 25% among dentate people. However, it is also possible that edentulous people represent a qualitatively different subset of individuals who, through genetic predisposition or some other mechanism, have an increased acute-phase response to any source of infection. In this study population, edentulous people were significantly older, more likely female, and had a lower income-poverty ratio compared with dentate people. In addition, a very large percentage of edentulous people had at least one of the five systemic risk factors for elevated CRP identified in Table 2. Conversely, the small numbers of edentulous people with none of those systemic risk factors contributed to large standard errors for their CRP

levels in the Fig., and it limited our ability to conduct additional analyses of this subgroup. Nonetheless, the multivariate analyses controlled for these conspicuous variations between dentate and edentulous people, so it is reasonable to conclude that there are real differences in CRP levels between edentulous persons and dentate persons with less extensive periodontal pocketing.

A possible explanation for the edentulism-CRP relationship is that edentulism is serving as a crude marker for an underlying trait that has persisted in individuals who, in years past, experienced severe oral disease due to that trait, and who rapidly lost their teeth as a consequence. If such a mechanism was predominant in the remainder of the population, it would mean that the periodontal-CRP association observed among dentate people was not causal, but rather that increases in both periodontal disease and CRP were a consequence of the trait. For example, based on epidemiological findings and results from *in vitro* and *in vivo* experimental studies, we have proposed a model in which periodontal disease may be linked to systemic inflammation through two main mechanisms (Beck *et al.*, 1996). One pathway of the model proposes that periodontal disease occurs as a joint response to local pathogens and to an underlying hyperinflammatory trait, which also causes elevation of systemic inflammatory mediators. However, an additional synergistic mechanism is proposed in which local periodontal infection creates an elevated systemic inflammatory response that potentiates the increase in CRP caused by systemic risk factors such as smoking, diabetes, and chronic bronchitis. Hence, the association observed in this analysis between periodontal pockets and CRP could be due to mechanisms operating through the latter pathway, while edentulism and CRP may be associated only by virtue of the underlying hyperinflammatory trait that produces the former pathway. However, it is not possible within the limitations of this cross-sectional analysis to determine which, if any, of these proposed causal pathways are responsible for the observed interrelationships among oral disease, systemic conditions, and inflammatory response in the US population.

Table 3. Logistic Regression Analysis of Prevalence of Elevated (≥ 10 mg/L) C-reactive Protein

Independent Variable[a]	df[b]	Wald F	P	Parameter	OR (95% CI)
Sex (ref = Male)	1	53.0	< 0.01	Female	2.94 (2.17 - 3.85)
Race/ethnicity (ref = White)	3	3.6	0.02	NH black	1.59 (1.20 - 2.11)
				Mex-Am	1.33 (1.02 - 1.73)
				Other	1.22 (0.75 - 1.99)
Pack-years of cigarettes	2	6.2	< 0.01	> 10	1.55 (1.20 - 2.01)
(ref = None)				1-10	1.25 (0.87 - 1.81)
Glycosylated hemoglobin	2	18.1	< 0.01	> 6.5%	3.37 (2.21 - 5.14)
(ref = < 5.7%)				5.7-6.5%	2.20 (1.52 - 3.18)
Chronic bronchitis					
history (ref = No)	1	6.9	< 0.01	Yes	1.83 (1.15 - 2.90)
No. of NSAIDs (ref = None)	2	6.4	< 0.01	> 25/month	1.47 (1.11 - 1.95)
				1-25/month	1.02 (0.79 - 1.32)
Pocket depth extent (Ref = 0%)	2	7.5	< 0.01	> 10%	1.87 (1.31 - 2.69)
				1-10%	0.98 (0.72 - 1.32)

[a] Additional independent variables included in this model were: age (7 categories), NHANES III examination phase (2 categories), and dental examiner (6 categories)m all of which were statistically significant (P < 0.01).
[b] For full model, -2 log likelihood = 25.1, df = 25, P < 0.01.

The clinical and public health relevance of "high-normal" CRP levels is based on epidemiological studies that have shown elevated CRP to be a risk factor for cardiovascular disease (Haverkate *et al.*, 1997; Ridker *et al.*, 1997). While the possible

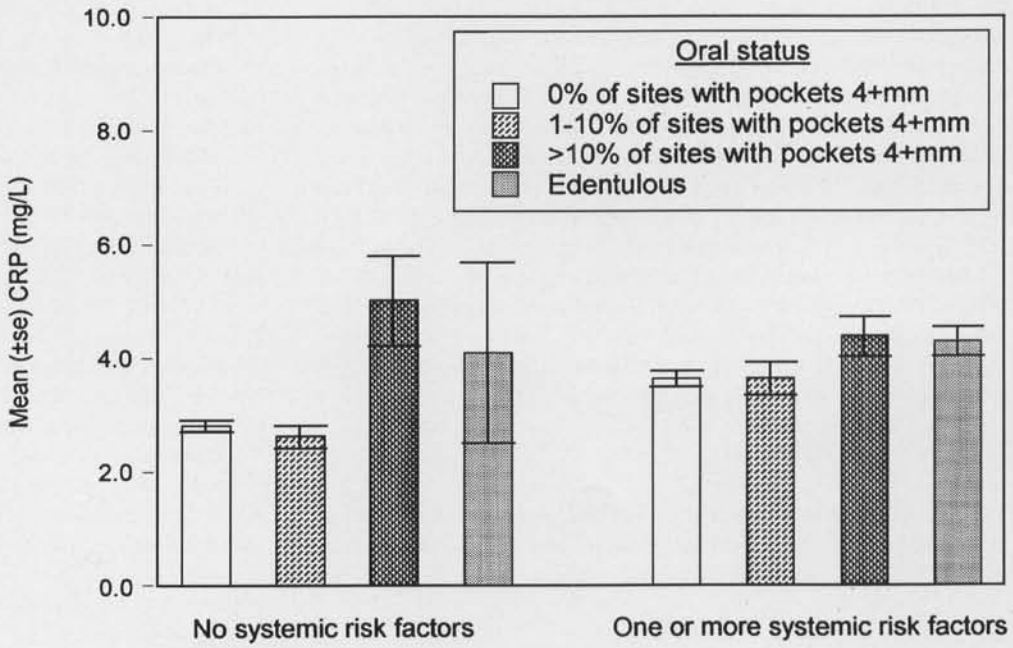

Figure. Variation in age-standardized CRP levels among oral status groups with and without one or more of five established risk factors for elevated CRP: glycosylated hemoglobin > 5.7%, arthritis history, bronchitis history, ever/current smoker; taking > 25 NSAIDs in previous month. Among people with no established risk factors, significant (P < 0.05) pairwise differences in mean CRP were observed between > 10% *vs.* 0% and > 10% *vs.* 1-10% groups. Among people with one or more established risk factors, significant (P < 0.05) pairwise differences in mean CRP were observed between > 10% *vs.* 0% and edentulous *vs.* 0% groups. Significant (P < 0.05) pairwise differences between groups with and without established risk factors for elevated CRP were observed for dentate people with 0% and for dentate people with 1 to 10% of sites with pockets 4+ mm.

mechanisms of CRP in cardiovascular pathology are uncertain, CRP is known to provide a protective role during the acute-phase inflammatory response by recognizing foreign pathogens and initiating their elimination, probably by activating the classic pathway of complement (Szalai *et al.*, 1997). Large amounts of CRP are produced by hepatocytes in response to circulating cytokines, such as TNFα and IL-1, produced at the site of tissue destruction. This CRP production by hepatocytes occurs at the expense of albumin and other constitutive proteins, a process labeled "reprioritization" of hepatic protein synthesis. However, competing demands for protein synthesis in cases of acute, overwhelming inflammation can lead to anomalous short-term changes in acute-phase reactants. For example, in a study of patients who experienced a 16-fold increase in CRP levels following major trauma, Petersen *et al.* (1977) observed reductions in CRP within four days of subjects' receiving nutritional and hormonal therapy, during which time other acute-phase reactants continued to increase. While these short-term discrepancies may be important considerations in the monitoring of temporal changes in the acute-phase response to major trauma, it seems unlikely that they would be sufficient to bias the current cross-sectional associations between periodontal disease and "high-normal" CRP levels.

While further research is needed to elucidate the causal mechanisms that are responsible for this observed association between oral conditions and systemic CRP, there are three main implications to be drawn from the current findings. First, periodontal disease needs to be viewed more broadly in terms of systemic inflammation, either as a consequence of an underlying hyperinflammatory trait or as a factor contributing to systemic inflammation. Second, there is a complementary need to recognize that "apparently healthy" individuals may nonetheless have extensive oral disease and raised CRP levels. Hence, oral disease assessments and systemic inflammatory response need to be incorporated into the signs and symptoms that define patients' overall health status. Finally, these findings suggest that retention of teeth, even if they have extensive periodontal pocketing, does not increase CRP levels beyond the levels observed for edentulous people in the US population (Fig.). Unlike the theory of focal infection that was used half a century ago as a popular justification for extraction of diseased teeth in the interests of systemic health (Meskin, 1998), the current findings indicate that the treatment of periodontal disease will require interventions that have a biological basis in periodontal medicine, rather than an empirical basis in dental surgery.

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