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C-reactive protein associated with periodontitis in a Thai population

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Abstract

Aim: C-reactive protein (CRP) has been implicated as a possible mediator of the association between periodontitis and several systemic diseases. Previous studies suggest an association between increased CRP levels and periodontitis predominantly in Caucasians. This study evaluated the associations of chronic periodontitis and *Porphyromonas gingivalis* with CRP in systemically healthy Thai adults.

Material and Methods: Serum high-sensitivity CRP was measured in 21 generalized periodontitis, 62 localized periodontitis, and 38 periodontally healthy control subjects. *P. gingivalis* in subgingival plaque samples was analyzed by polymerase chain reaction.

Results: Overall, these subjects had a median CRP level lower than that reported in the western populations. Subjects with generalized periodontitis and localized periodontitis had higher median CRP levels than controls (1.78 and 0.65 mg/l *versus* 0.25 mg/l, $p < 0.001$). Multivariate linear regression showed that log CRP levels were increased in subjects with generalized periodontitis ($p < 0.01$) and localized periodontitis ($p = 0.03$) compared with the controls, adjusted for age, body mass index and smoking. Presence of *P. gingivalis* was also independently associated with elevated log CRP levels ($p < 0.001$).

Conclusion: Periodontitis and subgingival *P. gingivalis* are associated with increased CRP levels. These findings suggest that periodontal infection may contribute to systemic inflammatory burden in otherwise healthy individuals.

Key words: acute-phase protein; C-reactive protein; inflammation; periodontitis; periodontal diseases; *Porphyromonas gingivalis*

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C-reactive protein (CRP) is a serological marker of systemic inflammation that has been associated with increased risk for various systemic diseases, including cardiovascular disease (CVD) (Ridker 2003) and adverse pregnancy outcomes (Tjoa et al. 2003, Pitiphat et al. 2005). Periodontitis has also been linked to elevated CRP levels in adults (Slade et al. 2000, Joshipura et al. 2004) and in pregnant women (Pitiphat et al. 2006). It is thus postulated that CRP might be a possible mediator of the association between periodontitis and these systemic conditions.

Race/ethnicity is known to affect CRP (Khera et al. 2005). Asian women in the US have significantly lower CRP levels than Black, White, and Hispanic counterparts (Albert et al. 2004). CRP levels were lower in Asian adults (Yamada et al. 2001, Charuruks et al. 2005) than that observed in western populations. These findings raise concerns for possible underestimation of risk for CVD in Asians, using the CRP risk categories recommended by the Centers for Disease Control and Prevention and the American Heart Association (Pearson et al. 2003). Most studies have examined the relation between periodontitis and CRP in predominantly Caucasian populations. Whether this association exists in populations with a low normal range of CRP is not well documented.

Several studies have investigated antibodies to various periodontal pathogens in relation to CRP, but the association has been reported consistently only for IgG to *Porphyromonas gingivalis* (Craig et al. 2003, Dye et al. 2005). Evidence is sparse on the association between a direct measure of periodontal

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pathogens and CRP, while it is more important because the presence of antibody titers is not necessarily indicative of an active infection. The presence of one or more species of subgingival periodontal bacteria was associated with increased CRP levels in cross-sectional studies (Noack et al. 2001, Bretz et al. 2005). These studies, however, did not report the relation of CRP to each specific bacterium separately. We therefore evaluated whether the association of periodontitis and the occurrence of *P. gingivalis* with CRP is present in a Thai population.

Material and Methods

Study population

The study was conducted in three centers: the Department of Periodontology at Khon Kaen University, Nam Phong Hospital and Khon Kaen Hospital in Khon Kaen, Thailand. The participants were a convenience sample of apparently healthy adults who attended these centres for an oral health examination. Exclusion criteria included: (1) known systemic disease, (2) regular use of medication, (3) presence of other infections or fever, (4) periodontal therapy in the past 6 months, (5) use of antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs) or mouth rinses in the past 3 months, (6) history of trauma or tooth extraction in the past month, (7) having less than 18 teeth, and 8) pregnant or lactating females.

The research protocol was approved by the institutional review boards of Khon Kaen University and the participating hospitals. All procedures were in accordance with the ethical standards for human experimentation established by the Declaration of Helsinki (World Medical Association 1997). Each participant provided informed consent before entering the study. We interviewed the participants for demographic and health-related information during the recruiting visit.

Measurement of periodontal status

Periodontal examination was performed by a trained and calibrated examiner (WS) in the dental clinics. Clinical parameters of periodontal disease evaluated in this study included probing depth (PD), clinical attachment level (CAL), and the presence of bleeding after 10 s of probing (BOP). The measurements were determined on six sites of all present teeth except the third molars.

We classified the participants according to their PD in three groups: control group (no site with PD $\geqslant$5 mm, $n = 38$), localized periodontitis group (1–30% sites with PD $\geqslant$5 mm, $n = 62$), and generalized periodontitis group ($>30\%$ sites with PD $\geqslant$5 mm, $n = 21$).

Plaque sampling

Subgingival plaque samples were obtained with sterile paper points inserted for 30 s into six selected sites from each patient. These sites were: the deepest subgingival sites of each sextant in periodontitis groups; and, in controls, the mesio-buccal site of teeth numbers 16, 11, 24, 36, 31 and 44, or the nearest tooth of the same type if any indicated tooth was missing. *Porphyromonas gingivalis* was detected by polymerase chain reaction (PCR).

PCR detection

Plaque samples were suspended in 1 ml sterile double-distilled water, pelleted, and resuspended in 200 μl of DNA isolation reagent (InstaGene Matrix, Bio-Rad Lab, Hercules, CA, USA). Total DNA was extracted according to the manufacturer's instructions. The suspension was centrifuged and 5 μl of resulting supernatant was used for PCR. The reactions were carried out as previously described (Ashimoto et al. 1996) using oligonucleotide primers specific for *P. gingivalis*. The PCR product was analysed by 1% agarose gel electrophoresis. Ten per cent of the PCR samples were tested in duplicate. The reproducibility of the duplicated samples was good with an agreement of 96%.

CRP measurements

Non-fasting blood samples were collected from participants at the time of clinical examination, and frozen at -70°C for future analysis. Serum CRP levels were measured using latex-enhanced nephelometry (N High Sensitivity CRP assay, Dade Behring, Marburg, Germany) on a BN 100 nephelometer (Dade Behring). One technician who was blinded to periodontal status of the participants performed all assays in one batch. This assay has a detection limit of 0.15 mg/l, an intra-assay coefficient of variation of 4.4%, and an inter-assay coefficient of variation of 5.7%. For participants who had a CRP value below the detection limit, we imputed a value of 0.075 mg/l (half of the detection limit).

Statistical analysis

We compared characteristics of the study groups using chi-square test or Fisher's exact test for categorical data, and analysis of variance for continuous data. Difference in CRP levels among groups was evaluated by Kruskal–Wallis and post hoc Wilcoxon tests with Bonferroni correction. The strength of the linear relationship between CRP and other factors was assessed by Spearman correlation.

To evaluate the associations of periodontitis and *P. gingivalis* with CRP, multivariate linear regression models were performed with log-transformed CRP levels as the outcome. We evaluated potential confounders by using the change-in-estimate method (Greenland 1989), with a cut-point of 10%. Potential confounders considered in these analyses were age, gender (male, female), educational level (college or above, secondary *versus* primary), body mass index (BMI), smoking status (current, past *versus* never), pack-years of smoking, and frequency of alcohol drinking ($\geqslant$1 drink/week or not). All statistical tests were two-tailed with a significant level of 0.05.

Results

The study groups were different in several characteristics. Compared with the controls, periodontitis subjects were older and less educated, were more likely to be males and current smokers, smoked more cigarettes, and had higher BMI (Table 1). As expected, there were significant differences in PD and CAL among the study groups, with generalized periodontitis subjects the highest and the controls the lowest (Table 2). Similarly, generalized periodontitis group had more sites with BOP or *P. gingivalis* than did the other groups. *P. gingivalis* was more prevalent in both periodontitis groups than in the controls ($p < 0.001$).

In this population, the overall median CRP level was 0.50 mg/l [interquartile range (IQR) 0.23–1.53]. The mean value was 1.37 (SD, 1.97) mg/l and ranged 0.08–11.2 mg/l. An undetectable level

Table 1. Characteristics of study participants by periodontal status

Characteristics	Periodontally healthy ($n = 38$)	Localized chronic periodontitis ($n = 62$)	Generalized chronic periodontitis ($n = 21$)	*p*-value
Age in years				
Mean ± SD	34.9 ± 8.3	40.4 ± 11.1	46.3 ± 10.1	<0.001
Min–max	20–52	20–66	31–67	
Male (%)	2.6	32.3	52.4	<0.001
Educational level (%)				0.001
Primary	13.2	37.1	61.9	
Secondary	50.0	50.0	23.8	
College or above	36.8	12.9	14.3	
Body mass index (kg/m^2)				
Mean ± SD	21.6 ± 2.4	23.6 ± 3.3	23.8 ± 3.2	0.002
Smoking status (%)				0.002
Current	2.6	12.9	23.8	
Past	0	16.1	14.3	
Never	97.4	71.0	61.9	
Pack-years of smoking				
Mean ± SD	0.03 ± 0.2	2.3 ± 5.4	4.3 ± 9.1	0.001
Alcohol consumption (%)				0.06
<1 drink/month	89.5	61.3	61.9	
1–3 drinks/month	7.9	16.1	19.1	
1–4 drinks/week	2.6	11.3	14.3	
⩾5 drinks/week	0	11.3	4.8	

SD, standard deviation.

Table 2. Clinical periodontal parameters, presence of *Porphyromonas gingivalis* and C-reactive protein (CRP) levels of the study participants by periodontal status

Characteristics	Periodontally healthy ($n = 38$)	Localized chronic periodontitis ($n = 62$)	Generalized chronic periodontitis ($n = 21$)	*p*-value
Probing depth (mm)				
Mean ± SD	2.19 ± 0.27	3.08 ± 0.47	4.23 ± 0.37	<0.001
Min–max	1.63–2.71	2.07–4.10	3.71–5.20	
Clinical attachment level (mm)				
Mean ± SD	2.14 ± 0.37	3.18 ± 0.87	4.91 ± 0.86	<0.001
Min–max	1.11–2.98	0.63–5.00	3.51–7.36	
% sites with bleeding on probing				
Mean ± SD	22.3 ± 13.9	56.0 ± 23.1	82.3 ± 12.3	<0.001
% sites with *P. gingivalis*				
Mean ± SD	11.8 ± 19.3	71.5 ± 36.9	87.3 ± 24.1	<0.001
Presence of *P. gingivalis* in subjects (%)	44.7	91.9	95.2	<0.001
CRP in mg/l				
Median (interquartile range)	0.25 (0.08–0.51)	0.65 (0.28–1.65)	1.78 (0.45–3.51)	<0.001
Mean ± SD	0.58 ± 0.93	1.54 ± 2.00	2.34 ± 2.69	
Subjects with CRP ⩾3 mg/l (%)	2.6	17.7	28.6	0.01

SD, standard deviation.

(<0.15 mg/l) was observed in 21 subjects (17.4%): two in generalized periodontitis, seven in localized periodontitis, and 12 in control groups. CRP was correlated positively with age ($r = 0.28$, $p = 0.002$), BMI ($r = 0.45$, $p < 0.001$), percentage of sites with *P. gingivalis* ($r = 0.39$, $p < 0.001$) and all periodontal parameters including PD ($r = 0.36$, $p < 0.001$), CAL ($r = 0.39$, $p < 0.001$), and percentage of sites with BOP ($r = 0.25$, $p = 0.005$).

Table 2 shows a positive association between periodontitis extent and CRP (Kruskal–Wallis, $p < 0.001$). Post hoc tests indicated that median CRP level was significantly higher in subjects with generalized periodontitis (1.78 mg/l, IQR 0.45–3.51, $p = 0.001$) and localized periodontitis (0.65 mg/l, IQR 0.28–1.65, $p = 0.001$) than in the controls (0.25 mg/l, IQR 0.08–0.51). The observed difference in CRP levels between the two periodontitis groups was not statistically significant ($p = 0.63$). There were more subjects with elevated CRP level (>3 mg/l) in both periodontitis groups than in the controls ($p = 0.01$).

In a multivariate linear regression analysis adjusted for age, BMI, and smoking, periodontitis remained positively associated with CRP (Table 3). Both the generalized periodontitis ($p < 0.01$) and the localized periodontitis ($p = 0.03$) groups had a significantly higher log CRP levels than the controls. Similarly, Table 4 shows a significant positive association of the presence of *P. gingivalis* with log CRP levels ($p < 0.001$), controlling for age, BMI, and smoking. Gender, educational level, and alcohol intake were not confounder in these analyses.

Discussion

This study demonstrated that periodontitis was independently associated with higher levels of CRP. A similar significant relation was observed between the presence of *P. gingivalis* and increased CRP levels controlling for age, BMI, and smoking. Chronic low-grade inflammation is thought to play a causal role in atherosclerosis and CVDs (Pearson et al. 2003). Our findings suggest that periodontal infection might be one of the underdiagnosed chronic inflammations contributory to systemic inflammatory responses, which in turn may increase the risk for CVDs.

In this study, median CRP levels were significantly higher in subjects with generalized periodontitis (1.78 mg/l) and localized periodontitis (0.65 mg/l) than in the controls (0.25 mg/l). These results were corroborated by a Dutch study that observed the highest median CRP level in generalized periodontitis patients (1.45 mg/l), while the levels in the localized periodontitis patients and the controls were 1.30 and 0.90 mg/l, respectively (Loos et al. 2000). Similar results were also found in a US study (Slade et al. 2000) which reported a mean CRP value of 4.5 mg/l in subjects with >10% of sites with PD ⩾4 mm, 3.4 mg/l in subjects with less extensive periodontal pocketing, and 3.3 mg/l in periodontally healthy subjects. These

Table 3. Multivariate regression model* of the association between chronic periodontitis and log C-reactive protein (CRP) levels in sera ($n = 121$)

Model	Log [CRP] (mg/l) $\beta \pm$ SE†	*p*-value
Intercept	-4.731 ± 0.838	< 0.001
Localized periodontitis	0.585 ± 0.269	0.03
Generalized periodontitis	0.962 ± 0.364	< 0.01
Age (years)	0.014 ± 0.011	0.21
Body mass index (kg/m^2)	0.137 ± 0.038	< 0.001
Past smoker	0.284 ± 0.374	0.45
Current smoker	-0.339 ± 0.355	0.34

*$R^2 = 0.28$.
†β, regression coefficient; SE, standard error.

Table 4. Multivariate regression model* of the association between presence of *Porphyromonas gingivalis* and log serum C-reactive protein (CRP) levels in sera ($n = 121$)

Model	Log [CRP] (mg/l) $\beta \pm$ SE†	*p*-value
Intercept	-5.07 ± 0.84	< 0.001
Presence of *P. gingivalis*	0.62 ± 0.28	0.03
Age (years)	0.02 ± 0.01	0.06
Body mass index (kg/m^2)	0.14 ± 0.04	< 0.001
Past smoker	0.35 ± 0.37	0.35
Current smoker	-0.16 ± 0.35	0.64

*$R^2 = 0.27$.
†β, regression coefficient; SE, standard error.

findings indicate a dose–response relationship between the extent of periodontitis and CRP.

The relation between periodontal disease extent and CRP is not unequivocal. A relatively large study of 1131 dentate elderly persons found no difference in CRP levels between individuals with extensive periodontitis (>10% sites with PD $\geqslant$6 mm) and individuals with intermediate or no disease (Bretz et al. 2005). Several aspects could potentially explain the lack of association. First, periodontitis in this study was measured approximately 12 months after blood sampling. This may bias the results towards the null although periodontal status was unlikely to change substantially during the time period. Second, this study described periodontitis using a threshold of PD $\geqslant$6 mm, which indicates severe periodontitis. It is therefore possible that subjects classified as no disease did actually have a less severe form of periodontitis which also raised CRP levels.

The present findings are consistent with previous reports (Noack et al. 2001, Buhlin et al. 2003), in which severity of periodontal breakdown was associated with CRP levels. In this study, the correlation between periodontal clinical parameters and CRP was modest, but significant, with the coefficients ranged between 0.25 and 0.39. These levels of correlation were similar to that observed in an earlier study (Buhlin et al. 2003).

Clinical signs of periodontal disease are a result of both bacterial infection and host response. Measures of infection, including quantifications of subgingival microorganisms and antibody responses to these pathogens, were suggested as a more direct measure of periodontitis for the studies of periodontal-systemic diseases association (Beck & Offenbacher 2005). Antibodies to *P. gingivalis* were consistently associated with increased CRP levels among a representative sample of US adults (Dye et al. 2005), American minorities (Craig et al. 2003), haemodialysis patients (Rahmati et al. 2002), and diabetics (Kuroe et al. 2004). Two studies also reported higher CRP levels in subjects with at least one species of subgingival periodontal pathogens as compared with pathogen-negative individuals (Noack et al. 2001, Bretz et al. 2005). To our knowledge, no prior study examined the relation between CRP and subgingival *P. gingivalis* specifically. Our results indicate that the presence of *P. gingivalis* in subgingival plaque, a probable indicator of current periodontal infection, was associated with periodontitis as well as increased CRP levels.

Evidence suggests that periodontal pathogens can penetrate gingival tissues and enter the bloodstream (Fives-Taylor et al. 1995, Lamont et al. 1995). Mastication, tooth brushing and dental procedures have been reported to initiate transient bacteremia in individuals with periodontitis (Guntheroth 1984, Kinane et al. 2005, Forner et al. 2006a). The presence of circulating oral bacteria or bacterial components may induce the production of inflammatory cytokines and CRP by the liver and other cells (Ide et al. 2004, Loos 2005, Forner et al. 2006b). Thus, *P. gingivalis* may contribute to the inflammatory burden directly and indirectly through CRP and cytokines.

P. gingivalis is only one of several microorganisms having a possible role in the association between periodontitis and CRP. There are also several subclassifications of *P. gingivalis*, which may vary in the level of virulence. However, the PCR method used to detect *P. gingivalis* in this study is unable to neither quantify the number nor identify subclassification of the bacteria. Further studies are therefore needed to confirm the association of CRP and periodontitis with other microorganisms, to evaluate whether the association between CRP and *P. gingivalis* differs among different subclassifications, and to determine whether increased CRP levels are correlated with increased number of *P. gingivalis*.

CRP levels observed in this study were similar to the reference values of apparently healthy Thai adults (Charuruks et al. 2005), which were lower than those generally reported in western populations. Interestingly, median CRP levels in the periodontitis groups in this study were similar to that observed in a Dutch study (Loos et al. 2000), even though the level in our control group was relatively lower.

Elevation of CRP >3 mg/l is an indicator of high risk for CVDs in adults (Pearson et al. 2003). In this study, the proportion of subjects with elevated CRP levels increased significantly from 2.6% in healthy controls to 17.7% in localized periodontitis group, and 28.6% in generalized periodontitis group. A previous study similarly reported a lower prevalence of elevated CRP in the controls (16.9%) than in the advanced periodontitis group (38.0%) (Noack et al. 2001). The lower proportion of individuals with high risk for CVD observed in the present study was possibly due to the lower normal range of CRP in our population.

This study has certain limitations. First, the study design was cross-sectional, it is thus impossible to determine the causality of the associations. We do not know if having periodontitis increases CRP levels or if high CRP levels make the individual more susceptible to periodontitis. We also do not know if the positive association between CRP, *P. gingivalis* and periodontitis is consistent over time in this population. Second, increases in CRP levels are non-specific. CRP is an indicator of a wide range of disease process including trauma, infections, and inflammation. To minimize these variations, we included in the study only apparently healthy individuals and excluded the participants if they had a history of infection, fever, trauma, or had taken medications within the recent past. Only one subject (in the generalized periodontitis group) in our study had CRP greater than 10 mg/l, a threshold level of acute-phase effect (Ridker 2003), limiting the possibility of increased CRP by acute infection or trauma. Exclusion of this subject from the analyses did not change the results materially (data not shown). CRP is also known to increase in diabetics (Pearson et al. 2003), but we did not examine glucose blood levels to identify incipient diabetics in this population. Third, like most other microbiological studies, we collected bacterial samples from a random sample of sites rather than full mouth. This may cause random misclassification, resulting in a weaker observed association between CRP and *P. gingivalis* than its actual association. Fourth, the CRP samples were not measured in duplicate. This too may cause random misclassification. Nonetheless, the significant associations of CRP with periodontitis and *P. gingivalis* were observed in this study despite these limitations.

In summary, our results demonstrate the associations of periodontitis and presence of *P. gingivalis* with elevated CRP levels, independent of age, BMI and smoking in a Thai population. These findings suggest that periodontal infection may contribute to systemic inflammatory burden in otherwise healthy individuals, even in a population with a low normal range of CRP.

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Clinical Relevance

Scientific rationale for the study: C-reactive protein (CRP) is a serological marker of systemic inflammation that has been implicated as a possible mediator of the association between periodontitis and several systemic diseases. Previous studies suggested an association of increased CRP levels and periodontitis in predominantly Caucasians. However, it is unclear whether the association exists in populations with a lower normal range of CRP or whether the presence of *P. gingivalis* in subgingival plaque is associated with increased CRP.

Principal findings: This study of systemically healthy Thai adults demonstrates the associations of chronic periodontitis and subgingival *P. gingivalis* with elevated CRP levels in sera, independent of age, BMI, and smoking.

Practical implications: Dentists should be aware that periodontal infection may contribute to systemic inflammatory burden, even in population with low normal range of CRP.