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Title: C-REACTIVE PROTEIN LEVELS IN GENERALIZED AGGRESSIVE
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Abstract

C-REACTIVE PROTEIN LEVELS IN GENERALIZED AGGRESSIVE PERIODONTITIS PATIENTS

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Background: There is mounting evidence to indicate that periodontitis may be a risk factor for cardiovascular disease (CVD). Periodontitis may be linked to CVD as either an etiologic mechanism or a predisposing factor that can hasten disease progression. Proinflammatory cytokines, elevated fibrinogen, and platelet aggregation are all potential mechanisms. The purpose of this study is to compare and review the serological differences in subjects with severe periodontitis, some of which involve established risk factors for atherosclerosis, particularly heightened C-reactive protein levels.

Methods: A total of 184 subjects, comprising of two periodontal subgroups, non-periodontal (NP = 91) and generalized aggressive periodontitis (SP = 93), had serum evaluated for C-reactive protein (CRP) levels using a high sensitive ELISA test. The CRP levels were compared against clinical and demographical data to include race, age, gender, number of teeth, probing depth, attachment level, bleeding index, plaque index, and gingival index.

Results: After adjusting for potential confounding variables, probing depth ($p < 0.001$) was the only variable found to be significant. In comparing the two subgroups, SP (3.73 mg/L with an upper limit of 10 mg/L) had a significantly elevated level of CRP as compared to NP (1.54 mg/L with an upper limit of 10 mg/L) group.

Conclusion: Pocket depth is significantly related to elevated levels of CRP, which is why it is imperative to treat periodontal pockets. This study may provide a possible link between CRP and periodontal disease, but a causal relationship cannot be inferred.

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Introduction

There is evidence that periodontitis and coronary artery disease are linked by inflammatory factors including C-Reactive Protein (CRP). CRP is an acute-phase reactant which responds to diverse inflammatory stimuli including heat, trauma, infection, and hypoxia. CRP levels provide useful information for the diagnosis, monitoring, and therapy of the inflammatory process and associated disease.^{1,2,3,4} CRP levels rise in serum or plasma within 24 to 48 hours following acute tissue damage, reach a peak during the acute stage (as high as a thousand-fold) and decrease with the resolution of inflammation or trauma.^{1,2}

C-reactive protein plays a key role in native immune response and is easily measured due to the long plasma half-life (12-18 hours).⁵ In healthy individuals, CRP levels are found in trace amounts with levels less than 0.3 mg/L.^{6,7,8} Serum levels of CRP could exceed 100 mg/L in the presence of overwhelming systemic infection, which provides a useful marker for tracking the course of the infection.⁹ However, Ridker showed that individuals free of systemic infection can still have moderately elevated CRP levels (>2.09 mg/L), suggesting that other pathological condition, may constitute an additional stimulus for a systemic inflammatory response among some individuals.^{9,10} One such process is periodontitis.

Periodontal disease is an 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 gingival and tooth roots that promote the overgrowth of anaerobic bacteria, and subsequent ulceration of the epithelium and destruction of collagen, periodontal

ligaments, and bone that forms the attachment between the jaw and tooth root. Factors contributing to periodontal disease include oral hygiene, individual host response, and the residential microflora.¹¹ Each of these may have a greater or lesser role depending on the type of periodontal disease and the individual.

Atherosclerosis and coronary artery disease (CAD) are chronic inflammatory disorders that are initiated by vascular injury induced by a number of factors. CAD is the number one cause of morbidity and mortality worldwide.¹² Recent studies showed that CRP is a strong predictor of future coronary artery events in healthy men and women. However, the relative risk of CRP is independent of other cardiovascular disease risk factors. Ridker et al. subdivided CRP levels into quintiles and found that the relative risks following adjustments for a first cardiovascular event for women were 1.4, 1.6, 2.0, and 2.3 for these respective quintiles (>0.45-1.08 mg/L, >1.08-2.09 mg/L, >2.09-4.19 mg/L, >4.19 mg/L).¹⁰ His study showed that CRP was a stronger predictor of cardiovascular events than LDL cholesterol. The predictive value of CRP levels above or below 3 mg/L in terms of first cardiovascular event, was similar to the predictive value associated with having or not having three or more characteristics of metabolic syndrome (upper-body obesity, hypertriglyceridemia, low HDL, hypertension, and abnormal glucose).⁵ Age-adjusted relative risks of future cardiovascular events for women in the low-CRP/no metabolic syndrome, high CRP/no metabolic syndrome, low-CRP/with metabolic syndrome, and high-CRP/with metabolic syndrome groups were 1.0 (referent), 1.5 (95% Confidence Interval 1.0 to 2.2), 2.3 (95% CI 1.6 to 3.3), and 4.0 (95% CI 3.0 to 5.4), respectively. Thus, CRP consistently added prognostic information to metabolic syndrome regardless of its severity in the prediction of future cardiovascular events.⁵

A correlation was found between elevated CRP and periodontal disease. CRP levels are elevated in subjects with periodontal disease and cardiovascular disease as compared to subjects with cardiovascular disease and no periodontitis. Noack et al found a significant increase in adjusted mean CRP levels in subjects with high attachment loss (4.06 ± 5.55 mg/L) as compared to control subjects (1.70 ± 1.91 mg/L).¹³

In our study, subjects with generalized aggressive periodontal disease were evaluated for levels of CRP compared with healthy control subjects. Generalized aggressive periodontal disease occurs in approximately 14% of the US population.¹⁴ Traditionally, CRP has been used clinically for diagnosis and monitoring of autoimmune and infectious diseases as well as treatments for these conditions. Routine laboratory methods for quantitation of CRP have reference ranges with upper limits of between 0.3 and 0.8 mg/dL. Recently, more sensitive assays have become available; these are termed high-sensitivity CRP (hs-CRP) assays, which are based on the principle of a solid phase enzyme-linked immunosorbent assay (ELISA).¹⁵ In prospective epidemiological studies, the hs-CRP assays are capable of quantifying low levels CRP and predict the relative risk of future coronary events for apparently healthy individuals.⁸

The purpose of this thesis is to compare and review the serological differences in subjects with generalized aggressive periodontitis, some of which involve established risk factors for atherosclerosis, particularly heightened C-reactive protein levels. Our study is to compare clinical parameters such as probing depth, attachment level, bleeding index, and gingival index to serum CRP levels. It is hypothesized that the data will demonstrate a correlation between CRP and increasing clinical parameters especially those associated with inflammation. We would expect generalized aggressive periodontal subjects to have

more generalized disease and therefore, have higher mean levels of CRP than healthy control subjects, and thus, a higher incidence of cardiovascular disease and atheromatous formation. Periodontal disease is a chronic inflammatory disease, and we therefore expect to have a direct correlation between clinical parameters and increasing levels of CRP after adjusting for known risk factors. Therefore, the data may provide insight on the relationship between periodontal disease and cardiovascular disease.

Materials and Methods

Patient Selection and Clinical Examination

All subjects were taken from the VCU Clinical Research Center for Periodontal Disease Database. The database, included patients referred to the center and patients identified from the dental population at VCU/MCV School of Dentistry. All patients signed an informed consent form approved by VCU Committee on the Conduct of Human Research. A total of 184 subjects had a medical history obtained by questionnaire and interview, complete dental exam, and matching serum samples with clinical exam. Complete exams consisted of suppuration index, plaque index (PI),¹⁶ gingival index (GI),¹⁷ pocket depth (PKT), bleeding index (BI), attachment loss measurements (AL), and tooth mobility. Missing and deciduous teeth were also recorded. Clinical exam was measured at 4 sites per tooth (mesio-buccal, buccal, distal-buccal, and lingual) with a Hu-Friedy color-coded probe (PCP 12). Diabetic subjects and subjects with reported arthritis were eliminated from the database. All examiners performing exams were calibrated to verify examiner reliability.¹⁸

Subject Groups:

Generalized Aggressive Periodontitis (SP). A total of 93 subjects with generalized pattern of severe periodontal destruction with attachment loss of at least 5 mm on eight or more teeth. Subjects ranged in age from 12 to 67 years of age.

Non-Periodontitis (NP) A total of 91 patients with no evidence of attachment loss, except for recession on the buccal of anterior teeth, at more than one site, or pockets greater than 3 mm. That is, no detectable periodontitis; healthy periodontium. Gingival inflammation may be present in variable degrees of severity. Subjects ranged in age from 6 to 50 years of age.

Quantitative Determination of C-reactive protein Concentration in Serum

Serum levels of CRP were quantified using a high sensitivity C-reactive protein enzyme immunoassay (hsCRP ELISA) test kit according to manufacturer's instructions (BioCheck, Inc., Burlingame, CA). Lower limits of hsCRP ELISA were approximately 0.1 mg/L CRP and the upper limits were 10 mg/L CRP. The test is based on the solid phase of ELISA and uses a unique mouse monoclonal anti-CRP antibody coated on micro tier wells used for solid phase immobilization. The antibody is directed against a distinct antigenic determinant on the CRP molecule. A goat anti-CRP antibody is in the antibody enzyme conjugate solution. Reacting with the two antibodies, the CRP molecules are sandwiched between the solid phase and enzyme-linked antibodies. After a 45-minute incubation at room temperature, the wells are washed with water to remove unbound labeled antibodies. A tetramethylbenzidine (TMB) reagent is added and incubated for 20 minutes, resulting in the development of blue color. The color development is stopped with the addition of 1N HCl resulting in a subsequent yellow

change in color. The concentration of CRP is directly proportional to the color intensity of the test sample. Absorbance is measured spectrophotometrically at 450 nm. All samples were run in duplicates.

Statistics

Groups were compared using either a chi-square statistic or by ANOVA. Tukey's HSD was used to distinguish groups after ANOVA identified a significant difference. Relationships between continuous variables were assessed using multiple regression. A significance level of 0.05 was used.

Results

Description of subjects

As seen in Table 1, two groups of subjects were studied (total n = 184). There were generalized aggressive periodontitis subjects (SP, n = 93) and non-periodontal subjects (NP, n = 91). Approximately 41% of all subjects were male. However, this percentage was different between the two groups (Fisher's exact, p-value = 0.0832). There were fewer males in the SP group. The race groups were different between the two groups (Fisher's exact, p-value = 0.0013). The SP subjects had a higher percentage of African Americans (61%) than the NP subjects (39%). The SP subjects had a higher percentage of confirmed smokers (41%, Fisher's exact p-value < 0.0001) than NP subjects (6%) The self-report measures of smoking showed similar differences (chi-square = 12.6, df = 2, p-value = 0.0018).

It was anticipated that subject groups would be different on clinical indices as well. The summary statistics for the two groups are shown in Table 2. The average age

was significantly different ($t = -0.40$, $df = 182$, $p = 0.6900$). The average number of teeth was significantly different ($t = 5.35$, $df = 181$, $p = <.0001$). As well, NP subjects had more teeth. The average pocket depth was significantly different ($t = -13.41$, $df = 181$, $p = <.0001$). SP subjects had deeper pockets. The average attachment loss was significantly different ($t = -13.90$, $df = 181$, $p = <.0001$). SP subjects had more attachment loss. The average PLI was significantly different ($t = -11.38$, $df = 182$, $p = <.0001$). SP subjects had more PII. The average BI was significantly different ($t = -9.87$, $df = 182$, $p = <.0001$). SP subjects had higher BI. The average GI was significantly different ($t = -14.10$, $df = 182$, $p = <.0001$). SP subjects had a higher GI.

Preliminary analyses

The intent of this thesis is to determine the relationship between CRP and the clinical characteristics of periodontal patients. First, the bivariate relationship between CRP and the clinical characteristics will be explored and then, in the next section, the multivariate relationship between CRP and the clinical characteristics will be described. In order to understand the bivariate relationship, it will also be necessary to determine whether the form of the relationship is constant across the two patient classifications.

Patient periodontal diagnosis:

In order to compare groups of subjects using ANOVA, one assumption is normality. The distribution of CRP is strongly skewed and so the log-transformed CRP values will be used in all analyses. The two patient groups were found to be significantly different ($t = 5.55$, $p < .0001$). The NP subjects had significantly lower values than the SP subjects (Table 3). Since subjects were intentionally sampled from each patient group, in addition to determining whether there is a relationship between CRP and the clinical

characteristics, there is also the possibility that the relationship is different depending upon the patient group.

Bivariate Analysis

The results presented below evaluate the relationship of CRP to individual clinical and demographical variables. The demographical variables sex, race, smoking status, and age demonstrated no evidence of a relationship when comparing levels of CRP to sex ($p = 0.5$), race ($p > 0.6$), and the three measures of smoking status: self-reported smoking status ($p > 0.7$), confirmed smoking status ($p > 0.2$), serum cotinine levels ($p > 0.8$), and age ($P > 0.7$) with patient's periodontal diagnosis was found. There is little evidence that there is a relationship between the number of teeth and CRP ($p > 0.09$) and the relationship does not seem to depend upon periodontal diagnosis ($p > 0.19$).

The clinical variable with a slight evidence for a significant relationship was between CRP and pocket depth ($p = 0.0788$). The relationship is the same in the patient groups ($p > 0.5$). There is no evidence a relationship was found depending upon patient's periodontal diagnosis between CRP and AL ($p > 0.6$), PLI ($p > 0.7$), and GI ($p > 0.5$). There is little evidence that BI is related to CRP ($p = 0.1076$) and the relationship does not change depending upon periodontal diagnosis ($p > 0.5$). More bleeding is associated with higher CRP.

Summary of Bivariate Analysis

Table 4 summarizes the relationships between the clinical variables and serum CRP. Note that at this stage on the preliminary analysis, the intent was to screen each of the variable for potential relationships and so a more liberal alpha level was chosen ($p <$

0.2). In summary, periodontal diagnosis, number of teeth, pocket depth, and BI were included in the final model building analyses.

Definitive analyses

In this section, all of the clinical variables are considered together to form the final model to describe relationships to CRP. As seen in Table 5, when all of the variables are considered together, many of them lose significance.

After removing any factor not significantly related to CRP (at $\alpha < 0.05$) only pocket depth and periodontal diagnosis was significantly related to log CRP (Table 6). This model indicates that the log CRP increases by 0.17 units for each mm increase in pocket depth. SP subjects are $2^{*.1275} = 0.255$ log CRP units higher. Figure 1 shows the relationship of pocket depth and periodontal diagnosis to CRP in its original units.

Discussion

A positive correlation between C-reactive protein and periodontal disease may be a possible underlying pathway in the association between periodontal disease and cardiovascular disease.¹³ Periodontal disease is a localized chronic inflammatory disease in which attachment loss is the determining factor. Attachment loss, as defined by the American Academy of Periodontology (AAP), is a measure of periodontal disease severity. Bleeding on probing is a sign of active tissue destruction and is a more sensitive sign of gingival inflammation than visual alterations. Bleeding index is useful for detecting early inflammatory changes and the presence of inflammatory lesions located at the base of the periodontal pocket. These two clinical parameters provide evidence that periodontal disease is significantly related to elevated levels of CRP.

In the present study, periodontal clinical parameters were evaluated for their relationship to CRP levels and its interaction with the severity of periodontal disease. We hypothesized that the generalized aggressive periodontitis (SP) group to have significantly elevated CRP levels as compared to the non-periodontal (NP) controls. After adjusting for potential confounding variables, log CRP was only significantly correlated to pocket depth ($p < 0.0001$) and periodontal diagnosis. Our model indicated that the log CRP increased by 0.17 units for each millimeter increase in pocket depth. This may be due to the increase in surface area for bacteria, plaque, and calculus to inflict a chronic infection. The clinical and demographical variables that lacked significance included race, age, gender, plaque index, gingival index, and attachment loss. No significant relationship was found between smoking status and age against elevated CRP levels, even though they have been demonstrated by previous studies to have a significant relationship with CRP. This may be due to patient unreliability and a low number of patients with high levels of CRP, which altered the mean levels of cotinine.

Our results confirmed the hypothesis that periodontal disease was significantly related to elevated CRP levels. SP (3.73 mg/L with an upper limit of 10 mg/L) group had significantly elevated levels of CRP as compared to NP (1.54 mg/L with an upper limit of 10 mg/L) group. When evaluating mean levels of pocket depths and bleeding index, it was found that SP subjects (3.53 mm and 0.48) had a higher mean average pocket depth (PD) and bleeding index (BI) than NP subjects (2.06 mm and 0.15), respectively. It is not unusual to find increased BI levels in SP subjects than NP subjects because most SP subjects have the disease. Data from figure 1 suggests that PD was more significant than

BI in their effect on CRP. When evaluating the clinical parameters against CRP and periodontal diagnosis, no interactions were found in any of the data.

Our data concurs with previous studies by Slade et al. ('00), Glurich et al. ('02), and Noack et al. ('01) in which there is a relationship between periodontal disease and elevated levels of CRP. Slade demonstrated that edentulism and periodontal disease were associated with increased CRP levels.⁹ In subjects with periodontal disease, the magnitude of the association was comparable with that identified for conditions such as chronic bronchitis and cigarette smoking. The study used the NHANES III database, which has inherent limitations, and CRP levels below 3 mg/L were not measured. Glurich found significantly elevated CRP levels in subjects with bleeding on probing and mean attachment loss of ≥ 4 mm.¹⁹ A correlation between elevated levels of CRP and cardiovascular disease was also demonstrated in subjects with periodontal disease as compared to subjects with cardiovascular and no periodontitis. Noack found a significant increase in adjusted mean levels of CRP in subjects with 3 mm mean attachment loss.¹³ In addition, CRP levels were not compared to other clinical parameters and no relationship was found between CRP and smoking.

Coronary artery disease remains a major cause of morbidity and mortality worldwide and 50% of the disease can be explained by known risk factors.¹² The other 50% remains unexplained, but periodontal disease may provide a partial explanation for the elevated risk of coronary artery disease. It has been shown in multiple prospective epidemiological studies that CRP may predict incident myocardial infarction,^{20,21,22,23,24,25} stroke,^{20,24,26,27} peripheral artery disease,²⁸ and sudden cardiac death²⁹. In fact, CRP has been shown to be a stronger predictor of cardiovascular events than LDL cholesterol,

which only provides 3 to 5 percent of the variance for CRP.¹⁰ Ridker et al. subdivided CRP into quintiles and found the relative risks following adjustment for a first cardiovascular event for women were 1.4, 1.6, 2.0, and 2.3 for three respective quintiles (>0.49-1.08, >1.08-2.09, >2.09-4.19, >4.19).¹⁰ Our mean CRP levels were 1.54 and 3.73 for NP and SP groups, respectively. Unfortunately, we are unable to infer any conclusions because two different methods were used to measure CRP levels. We excluded subjects with CRP levels greater than 10 mg/L due to the assumption that they have an acute infection. The infection may take up to three weeks to resolve prior to CRP levels returning to baseline.

The results of these studies provide a possible link between CRP and periodontal disease, but a causal relationship cannot be inferred. An inherent limitation is the fact that these studies are mainly cross-sectional and not long-term cohort studies, which limits the comparison of each variable over time. Therefore, it is not statistically possible to infer if the pocket depth or an elevated CRP was the inciting event.

Future studies may establish a relationship between periodontal disease and elevated CRP levels, which can evaluate the effect of periodontal therapy on CRP levels and therefore, reduce CAD risk. In subjects with increased hs-CRP concentration, aspirin and Prevastatin are effective in decreasing the incidence of future coronary events.³⁰ Periodontal therapy will help maintain oral health which may affect systemic health and thus reduce the risk of developing a first cardiovascular event. From our study, we can only conclude that pocket depth is significantly related to elevated levels of CRP, which is why it is empirical to treat periodontal pockets. The data indicates that the patient's

overall health status and prevention of the hyperinflammatory state must be considered by providing treatment and limiting the source of inflammation.

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Table1

Description of categorical variables for each patient classification

Variable	Patient Classification			
	NP (n = 91)	SP (n = 93)	total (n = 184)	
Sex	F	44 (48.4)	64 (68.8)	108 (58.7)
	M	47 (51.6)	29 (31.2)	76 (41.3)
Race	B	34 (37.4)	57 (61.3)	91 (49.5)
	W	57 (62.6)	36 (38.7)	93 (50.5)
Smoker (confirmed)	N	49 (94.2)	43 (58.9)	92 (73.6)
	Y	3 (5.8)	30 (41.1)	33 (26.4)
Smoker (self-report)	F	0 (0.0)	6 (6.5)	6 (3.3)
	N	53 (58.2)	34 (36.6)	87 (47.3)
	Y	38 (41.8)	53 (57.0)	91 (49.5)
	total	91	93	184

F=female, M = male, B=Black, W=White, N=nonsmoker, Y=smoker, F=former smoker

NP = non-periodontal, SP = generalized aggressive periodontitis

Table 2

Description of continuous variables for each patient classification

Class	n	Age (at blood draw)			
		Mean	SD	Range	
NP	91	30.66	8.15	6.75	52.17
SP	93	31.13	7.76	12.51	66.72
No. Teeth					
NP	90	27.74	2.55	16.00	32.00
SP	93	24.30	5.57	6.00	32.00
Pocket depth					
NP	90	2.06	0.24	1.61	2.73
SP	93	3.53	1.01	2.01	8.05
Attachment loss					
NP	90	0.21	0.26	0.00	1.72
SP	93	2.70	1.68	0.20	9.07
PLI					
NP	91	0.47	0.39	0.00	2.19
SP	93	1.25	0.53	0.05	2.54
BI					
NP	91	0.15	0.17	0.00	0.85
SP	93	0.48	0.26	0.00	1.00
GI					
NP	91	0.57	0.33	0.09	1.40
SP	93	1.42	0.48	0.38	2.55
Cotinine					
NP	52	33.55	99.58	0	589
SP	73	202.22	291.48	0	1377

NP=non-periodontal, SP=generalized aggressive periodontitis,
 PD and AL reported in mm's, PII and GI reported on 0-3
 scale, BI reported as 0 or 1, Cotinine reported ng/mL

Table 3

Comparison of CRP levels between the two patient groups

	n	CRP			
		Mean	SD	Range	
NP	91	1.54	2.03	0.03	10.07
SP	93	3.73	3.43	0.07	14.04

NP=non-periodontal, SP=generalized aggressive periodontitis
 CRP reported as mg/L

Table 4

Summary of Bivariate Relationships to CRP

Factor	p-value
Class	<.0001 *
Sex	0.3292
Race	0.3613
SmokerY/N	0.5934
ConSmoker	0.5381
Log Cotinine	0.9192
Age	0.2726
No. Teeth	0.0964 *
Pocket depth	0.0788 *
Attachment loss	0.2531
PLI	0.3133
GI	0.8206
BI	0.1076 *

* potentially related, $p < 0.2$.

class = periodontal diagnosis

Table 5

ANOVA results including all potentially significant predictors

Effect	df	MS	F	p-value
Model	4	3.672	10.43	<.0001
Class	1	0.819	2.3269	0.1289
No. Teeth	1	0.42	1.1928	0.2762
Pocket depth	1	1.962	5.5734	0.0193
BI	1	0.082	0.2318	0.6308
Error	178	0.352		

class = periodontal diagnosis

Table 6

ANOVA results for significant predictors of log CRP

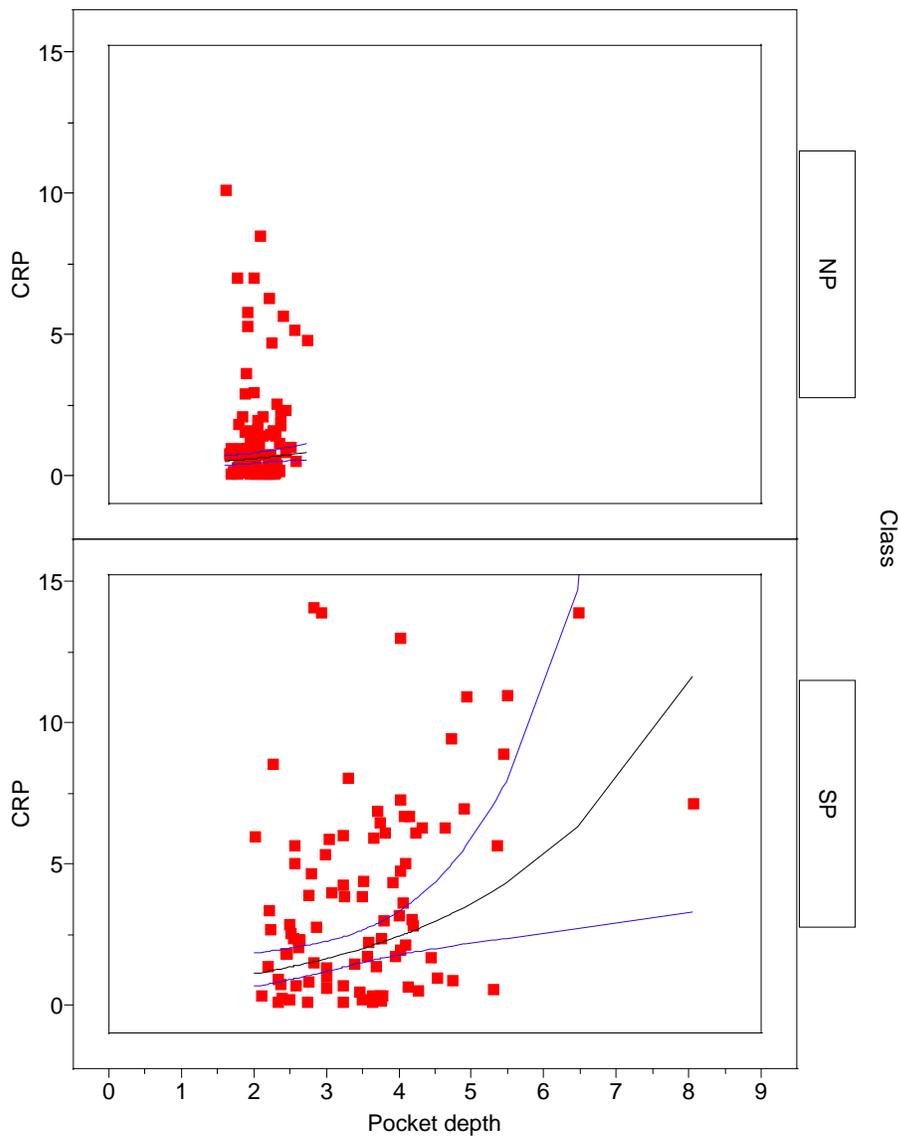
Effect	df	MS	F	p-value
Model	2	7.104	20.25	<.0001
Class	1	1.492	4.2523	0.0406
Pocket depth	1	2.765	7.8813	0.0055
Error	180	0.351		

Significance established at $p < 0.05$

class = periodontal diagnosis

Figure 1

Plot of the Relationship with Pocket Depth and Patient periodontal diagnosis



• **CRP** — Predicted CRP — Lower 95% CI — Upper 95% CI
 class = periodontal diagnosis
 NP = non-periodontal
 SP = generalized aggressive periodontitis