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ARTIGO

SEVERE CHRONIC PERIODONTITIS AND C-REACTIVE PROTEIN LEVELS
PERIODONTITE CRÔNICA GRAVE E NÍVEIS DE PROTEÍNA C-REATINA

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RESUMO

Este estudo avaliou a relação entre periodontite crônica grave e proteína c-reativa (PCR) considerando alguns fatores associados. Este estudo transversal incluiu 75 indivíduos adultos, aparentemente saudáveis, de ambos os sexos. Após entrevista, os participantes foram submetidos a exames físicos, odontológico e coleta de sangue. Avaliação de PCR foi feita através de nefelometria. Exame clínico periodontal foi realizado por examinadores treinados e o diagnóstico de periodontite crônica foi estabelecido quando o indivíduo apresentasse pelo menos 30% dos dentes com nível de inserção clínica ≥ 5 mm. Análise descritiva e de regressão linear múltipla foram realizadas. Os resultados mostraram que não houve diferença estatisticamente significante nos níveis de PCR entre os grupos com e sem periodontite. A mediana dos níveis de PCR no grupo com periodontite foi de 2,3 mg/l (intervalo interquartil 25-75%, IQR = 0,74-5,4) e no grupo sem periodontite, 1,8 mg/l (25-75% IQR = 0,79-4,54) (p = 0,417). Os valores de log da PCR foram significativamente correlacionados apenas com índice de massa corporal do indivíduo (IMC). Os principais resultados deste estudo indicam que não há associação entre a periodontite crônica grave e PCR, e fatores como IMC precisam ser analisados com cuidado em estudos sobre este tema.

Palavras-chave: Periodontite; Proteína C-reativa; Resposta inflamatória.

ABSTRACT

This study aims to analyze the relationship between chronic periodontitis and C-reactive protein (CRP), taking certain associated factors into consideration. A cross-sectional study was conducted on a sample of 75 adults of both sexes. After the participants had been interviewed, they underwent physical and dental examinations and blood collection. CRP levels were evaluated by means of nephelometry. A periodontal clinical examination was conducted by trained examiners and the diagnosis of chronic periodontitis was established when at least 30% of the individual's teeth presented clinical attachment loss ≥ 5 mm. The analysis procedures consisted of descriptive analysis and linear regression. The results showed that there was no statistically significant difference in CRP levels between the groups with and without periodontitis. The median CRP level in the group with periodontitis was 2.3 mg/l (25-75% interquartile range, IQR = 0.74-5.4) and in the group without periodontitis, 1.8 mg/l (25-75% IQR = 0.79-4.54) (p = 0.417). Log CRP was significantly correlated only with the individual's body mass index (BMI). The main findings from this study indicate that there is no association between severe chronic periodontitis and CRP, and factors like BMI need to be analyzed carefully in studies on this topic.

Keywords: Periodontitis; C-reactive protein; Inflammatory response.

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INTRODUCTION

Since the beginning of the 20th century, the linkage between oral infections and systemic conditions has been under discussion. This theory, which was initially named "Focal Infection" gave rise to a line of research named "Periodontal Medicine", which has attracted the attention of many researchers and clinicians. The main mechanisms for this interaction involve migration of oral bacteria and their byproducts to the bloodstream, thereby establishing chronic systemic inflammatory conditions[1], and exacerbation of local inflammation, which is induced primarily by periodontal pathogenic bacteria, via circulating systemic inflammatory mediators[2].

Among oral diseases, periodontal disease is the second most prevalent type worldwide and, given its infectious and inflammatory nature, it has become a serious public health problem. This has become especially evident because of its distant repercussions, such as premature and low weight births, respiratory infections, diabetes and cardiovascular diseases[3,4,5,6].

Among the inflammatory products of periodontal disease that are involved in damage at a distance from the oral cavity, C-reactive protein (CRP) can be highlighted. This is one of the plasma proteins from the acute phase of the inflammation produced by hepatocytes. It is currently used as a marker for future cerebrovascular and cardiac events and disorders, since it induces endothelial alterations and contributes towards formation of atheromatous plaque[7,8].

Tests for CRP have been shown to be clinically very useful for identifying individuals with acute inflammation. They enable monitoring of therapeutic responses and consequently enable changes to the treatment aims. According to the Centers for Disease Control and Prevention and the American Heart Association, CRP levels > 3 mg/l indicate a high risk of cardiovascular diseases, while 1 to 3 mg/l suggests medium risk and < 1 mg/l suggests low risk[9,10].

In the literature, a variety of factors determining elevation of plasma CRP levels have been highlighted, such as aging, alcohol consumption, smoking, sedentary lifestyles, obesity, presence of diabetes, high triglyceride levels, estrogen intake, sleep disorders and depression[4]. Furthermore, some studies have suggested that high CRP levels not only may be due to acute infections but also may reflect chronic health problems and behavioral problems and may be associated with poor socioeconomic conditions, even in apparently healthy individuals[11,12,13].

From this perspective, some studies have affirmed that high CRP levels may be related to greater severity of periodontal disease and to the presence of periodontal pathogenic bacteria[14,15,16,17,18,19]. The basis for such affirmations is the observed direct action of lipopolysaccharides (released during the periodontal inflammatory process) on hepatocytes, with consequent stimulation of cytokines.

However, there have been inconsistencies in the findings published in the literature. These have largely been due to interference from covariables that were not properly controlled for, such as age, smoking, body mass index and socioeconomic condition. Thus, given the importance of identifying the potential determinants of high serum CRP levels, and consequently of cardiovascular events, as well as the limited number of studies analyzing the influence of interfering factors, the present study had the objective of comparing the CRP levels between individuals with and without severe chronic periodontitis, taking certain associated factors into consideration.

METHOD

Study participants

The methodology for this study consisted of a cross-sectional investigation conducted on two convenience samples of different socioeconomic levels, with the main aim of assessing the influence of socioeconomic condition on inflammatory state. Out of a total of 150 individuals in the database[20], 75 adults of both sexes were included in this study. They all had a minimum of six teeth in their mouth and periodontal clinical records.

The group of low socioeconomic level was composed of the parents of students at the Amélia Rodrigues public school, located in Monte Gordo, a district of the municipality of Camaçari, in the state of Bahia. This is a peripheral area within the Metropolitan Region of Salvador, at a distance of 42 km from the state capital. This city houses the Camaçari Petrochemical Complex and a Ford car assembly plant, and it has an urban way of life, which makes it possible to infer that the individuals of low socioeconomic level in this region do not differ from individuals of low socioeconomic level in the city of Salvador. In turn, the group of high socioeconomic level was formed by the parents of students at the Bahia School of Medicine and Public Health, which is located in the city of Salvador.

It should be noted that this socioeconomic contrast between the groups in Monte Gordo and Salvador was proven through the data presented by in a previous study on the same database, i.e. predominance of socioeconomic classes C, D and E in the group in Monte Gordo (99%), and low schooling levels compared with the group in Salvador[20].

Data-gathering procedures

Initially, letters were sent out to the parents of both groups, inviting them to participate voluntarily in the study. After accepting, each participant was interviewed at the offspring's school, using a structured questionnaire with questions on sociodemographic, health condition and lifestyle factors. Histories of diabetes, hypertension, lipid disorders, cholesterol treatment, smoking habit, alcohol consumption, hormone

therapy use, sedentary lifestyle and myocardial infarction in the family were investigated, along with ascertaining their menopausal condition, weight and height.

On the same day that each individual was interviewed, he or she also underwent physical and dental examinations and blood samples were collected to measure the blood glucose, lipid and CRP. In addition, all the subjects were asked to report any occurences of acute inflammatory processes, such as colds, pharyngitis, symptoms of urinary infection, acute diarrhea or fever, on the day when CRP data were gathered.

This study was approved by the Ethics Committee of the Science Development Foundation of Bahia, Salvador, Bahia, Brazil (Protocol No. 65/2005), and all the participants signed a free and informed consent statement.

Clinical diagnosis of periodontal disease

The periodontal clinical examination was conducted by previously trained examiners, and individuals were considered to present severe chronic periodontitis when at least 30% of their teeth had at least one examination site with clinical attachment loss $\geq$ 5 mm[21]. From this criterion for periodontal disease, groups with and without periodontitis were defined.

The probing depth procedures were carried out and recorded at six sites for each tooth present in the mouth (with the exception of the third molars). These sites consisted of four proximal measurements (mesiovestibular, mesiolingual, distovestibular and distolingual), one measurement in the medial-vestibular region and one measurement in the medial-lingual region. All the measurements were made using a Williams probe graduated in millimeters (Hu-Friedy, USA), which indicated the distance from the gingival margin to the most apical extent of the probing depths. Measurements of gingival recession and clinical attachment loss were also obtained at the abovementioned sites. The gingival recession measurement comprised the distance from the gingival margin to the cement-enamel junction, and the clinical attachment loss was the result from summing the values of the probing depth and the recession measurement.

C-reactive protein test

The CRP level was assessed using a sample of 10 ml of peripheral blood, which was obtained by means of venous puncture, in conjunction with the immunonephelometry technique, using anti-CRP monoclonal antibodies, thus enabling quantitative results (mg/l). All the tests were performed in the same laboratory, under standardized conditions.

Data analysis

The independent variable was severe periodontitis and the dependent variable was the CRP level. The CRP values were firstly transformed into their $\log_{10}$ equivalents, given that the results did not show normal distribution, and then other associations were analyzed. The following covariables were taken into consideration in the analysis: sex, age, skin color, marital status, body mass index, blood glucose, hypertension, schooling level and socioeconomic level. The latter was categorized according to the study localities, i.e. Monte Gordo as low socioeconomic level and Salvador as high socioeconomic level. Each individual's socioeconomic profile was also analyzed in accordance with the Brazilian economic classification criteria of the Brazilian Association of Polling Companies (Associação Brasileira de Empresas de Pesquisa, ABEP). This made it possible to stratify the population into five economic classes (from A to E).

Preliminary descriptive analyses were made by means of bivariate models using the chi-square or Fisher test (for categorical variables) and the T or Mann-Whitney test (for continuous variables), depending on whether the distribution was normal, to compare the covariables investigated between the groups with and without periodontitis. If categorization of continuous variables was required, this was done based on the distribution or using cutoff points in accordance with data in the literature. Differences were considered to exist when $p < 0.05$.

Associations between CRP and certain variables were investigated using Spearman correlation analysis. Multiple regression analysis was performed using the backward method, to estimate the differences in mean log-transformed CRP values between the groups with and without periodontitis, with adjustment for potential confounding variables. Variables with statistical significance less than 20% were selected for the regression model. Interactions were ascertained using the partial F test, by comparing models with and without the product term.

In the data analysis, the STATA software (version 8.0) and SPSS software (version 10.0) were used, and the significance level was taken to be 5% in all the analyses performed.

RESULTS

Among the 75 individuals in the sample, one of them reported having had acute myocardial infarction, six had had angina and one had suffered a stroke. The participants' mean age was 46 years, with a minimum of 34 years and maximum of 80 years. The proportion of the individuals with at least 30% of their teeth presenting a minimum of one site with a clinical attachment loss $\geq$ 5 mm in the sample was 32%.

The sociodemographic and health condition characteristics of the individuals with and without periodontitis are shown in **Table 1**. In the group with periodontitis, the mean age was slightly greater, with greater proportions of men and individuals of black or mixed skin color, without partners, with low socioeconomic level (represented by the locality of Monte Gordo, and consequently of social classes C, D or E), with not more than four years of schooling, with reports of acute or chronic inflammatory conditions and with hypertension, in

comparison with the group without periodontitis. With regard to lifestyle, also in this same comparison between the groups, it was noted that there was a greater proportion of smokers, lower frequency of alcoholic drink consumers and greater proportion with sedentary habits. However, these differences were only significant for the presence of hypertension (p = 0.002) and alcohol consumption (p = 0.028). The difference in age between the groups was at the threshold (p = 0.058).

In relation to clinical/laboratory and periodontal characteristics (**Table 2)**, it was observed that the means for CRP (4.5 mg/l), probing depth (2.8 mm), clinical attachment loss (4.0 mm), bleeding on probing (38.5%), body mass index (28 kg/m^2) and blood glucose (93.9 mg/l) were higher in the individuals with periodontitis. The mean number of teeth present in the mouth (17.9) and mean levels of HDL cholesterol (50.3 mg/l) and LDL cholesterol (123.9 mg/l) were greater in the group without periodontitis. However, these differences were only significant for the clinical descriptors of probing depth and clinical attachment loss (p < 0.001) and the number of teeth present (p = 0.008).

Table 1. Sociodemographic and lifestyle characteristics of the study participants according to periodontal condition (≥ 30% of the teeth with at least one site presenting clinical attachment loss ≥ 5 mm).

Characteristics	With Periodontitis (N = 26)	Without Periodontitis (N = 49)	P
Age (years; mean ± sd)	49.3 ± 11.7	44.7 ± 8.55	0.058
Min - Max (years)	30 - 81	28 - 67	
Sex			
Female	17 (65.4)	39 (79.6)	
Male	9 (34.6)	10 (20.4)	0.178
Skin color (n [%])			
White	5 (19.2)	12 (24.5)	
Nonwhite	21 (80.8)	37 (75.5)	0.605
Conjugal situation (n [%])			
With partner	17 (65.4)	35 (71.4)	
Without partner	9 (34.6)	14 (28.6)	0.589
Socioeconomic level (locality; n [%])			
High (Salvador)	5 (19.2)	15 (30.6)	
Low (Monte Gordo)	21 (80.8)	34 (69.4)	0.289
Social class (ABEP; n [%])			
A/B	6 (23.1)	16 (32.7)	
C/D/E	20 (76.9)	33 (67.3)	0.386
Schooling level (n [%])			
> 4 years	9 (34.6)	20 (40.8)	
≤ 4 years	17 (65.4)	29 (59.2)	0.600
Acute/chronic inflammatory condition or parasitosis**			
No	12 (54.5)	21 (65.6)	
Yes	10 (45.5)	11 (34.4)	0.412
Hypertension (n [%])			
No	14 (53.8)	39 (79.6)	
Yes	12 (46.2)	10 (20.4)	0.02
Smoking habit (n [%])			
No	23 (88.5)	46 (93.9)	
Yes	3 (11.5)	3 (6.1)	0.412
Alcohol consumption (n [%])			
No	21 (80.8)	27 (55.1)	
Yes	5 (19.2)	22 (44.9)	0.028
Physical activity level			
Active	17 (65.4)	35 (71.4)	
Sedentary	9 (34.6)	14 (28.6)	0.589

* p-value calculated using the chi-square and Fisher tests (p ≤ 0.05).
** excluding the 22 individuals who did not present any acute/chronic inflammatory condition or intestinal parasitosis.

Table 2. Clinical and periodontal characteristics of the study participants according to periodontal condition.

Characteristics	With Periodontitis (N = 26)	Without Periodontitis (N = 49)	p*
CRP (mg/l; mean ± sd)	4.5 ± 5.3	3.2 ± 3.9	0.350
Min – Max	0.3-20.5	0.1-22.1	
Probing depth (mm; mean ± sd)	2.8 ± 0.7	2.0 ± 0.5	<0.001
Min – Max	1.8-5.0	0.0-2.7	
Clinical attachment loss (mm, mean ± sd)	4.0 ± 1.3	2.3 ± 0.5	<0.001
Min – Max	2.3-6.9	0.5-3.0	
No. of teeth presents (n, mean ± sd)	17.9 ± 6.4	22.1 ± 6.4	0.008
Min – Max	6-32	7-32	
Bleeding on probing (%, mean ± sd)	38.5 ± 25.7	11.0 ±14.5	< 0.001
Min – Max	0.0-100.0	0.0-58.6	
Body mass index (kg/m^2, mean ± sd)	28.0 ± 4.9	26.6 ± 4.6	0.229
Min – Max	19.5-38.9	19.7-38.5	
Blood glucose (mg/dl, mean ± sd)	93.9 ± 35.9	78.4 ± 7.5	0.080
Min – Max	67-215	60-98	
HDL cholesterol (mg/dl, mean ± sd)	48.9 ± 13.8	50.3 ± 12.3	0.659
Min – Max	30-101	30-87	
LDL cholesterol (mg/dl, mean ± sd)	120.7 ± 32.3	123.9 ± 32.4	0.691
Min – Max	45.2-174.2	66.8-206.0	

* p-value calculated using t and Mann-Whitney tests (p < 0.05).

In the Spearman correlation analysis (**Table 3)**, CRP log values were significantly correlated only with the individual's body mass index (BMI). The median CRP level in the group with periodontitis was 2.3 mg/l (25-75% interquartile range, IQR = 0.74-5.4) and in the group without periodontitis, 1.8 mg/l (25-75% IQR = 0.79-4.54), with overlapping of the

IQRs and without any significant difference (p = 0.417) **Figure 1**. Nevertheless, it was observed that the upper limit of the IQR of the group with periodontitis was higher than that of the control group. Even after removing the influence of outliers, there was no change to the results.

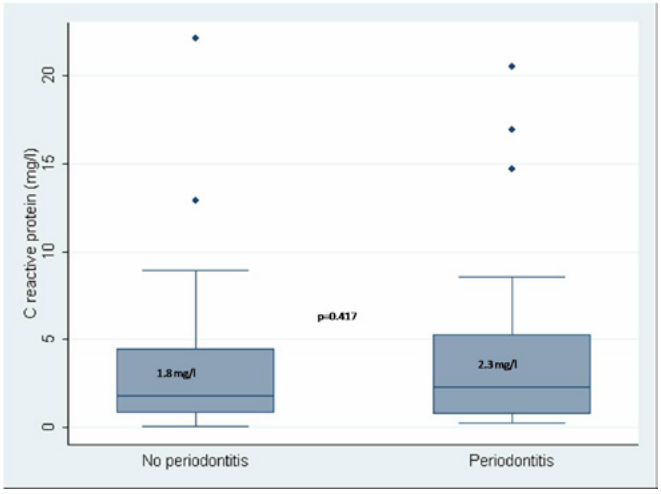

Figure 1. Box plot for C-reactive protein between the groups with and without periodontitis.

Table 3. Bivariate analysis between log CRP and certain clinical variables.

Variables	Log CRP	
	R	*P**
Clinical attachment loss	-0.014	0.905
Bleeding on probing	0.009	0.940
% of teeth with clinical attachment loss ≥ 5 mm	-0.010	0.934
HDL	-0.074	0.526
LDL	0.134	0.252
Blood glucose	0.146	0.210
Body mass index	0.406	0.000
Age	0.023	0.844

* p-value significant at 5%.

In the linear regression analysis, the possible interacting variables were investigated, along with the possible confounders selected from the empirical data (hypertension and alcohol consumption) or according to their epidemiological relevance, as stated in the literature (blood glucose, smoking habit, sex, age and socioeconomic condition). None of the covariables were shown to be effect modifiers. Only blood glucose presented a large impact as a confounding variable (40%), along with body mass index (29%) and socioeconomic condition (22%).

Table 4 shows different regression models for the main association between severe chronic periodontitis and CRP. It was observed that the lack of statistically significant difference in mean log CRP value between individuals with and without periodontitis was maintained from the univariate model to the final model adjusted for body mass index, blood glucose and socioeconomic condition.

Among the factors interfering in this association, body mass index can be highlighted. This was shown to be significantly correlated with the mean log CRP values (p = 0.001).

DISCUSSION

The findings from the present study showed that there was no statistically significant difference in CRP values between the groups with and without severe periodontitis. On the other hand, the median and the upper limit of the IQR of the CRP values were higher in the group that presented severe periodontitis than in the control group.

Certain limitations of the present study may have interfered in these results and deserve to be highlighted. Firstly, the main limitation relates to the small number of individuals studied and the low power for estimating differences beyond chance occurrences. Another point relates to the cross-sectional study design used, which weakens the causal inferences, given that temporality is compromised. In addition, the CRP level was assessed at a single time, thus neglecting within-individual variability. Thus, prospective studies would be ideal for assessing the influence of chronic diseases like periodontitis on serum CRP levels.

In this study, two individuals presented CRP levels greater than 20 mg/l (22 mg/l in the group without periodontitis; and 20.5 mg/l in the group with periodontitis), thus suggesting that acute inflammation or recent trauma was present. Exclusion of these individuals from the sample did not modify the results (data not presented). It should also be noted that the median number of individuals with severe periodontitis was below the level that is considered to present

Table 4. Linear regression models for the association between severe chronic periodontitis and log CRP.

	Univariate model				Final model			
	ß	95% CI	P > t	exp (ß1)	ß	95% CI	P > t	exp (ß1)
Severe chronic periodontitis	0.144	(-0.152; 0.441)	0.333	1.13	0.093	(-0.171; 0347)	0.479	1.10
Body mass index					0.047	(-0.022 ; 0.335)	0.001	
Blood glucose					-0.002	(-0.008; 0.003)	0.352	
Socioeconomic level					0.059	(-0.225; 0.370)	0.628	

high risk (CRP > 3 mg/l), thus remaining within the range of medium risk of cardiovascular disease (1 to 3 mg/l), together with the individuals who were considered to be without periodontitis. In view of the small sample size, it was not possible to stratify the study group according to the severity of periodontal disease (mild, moderate or severe), and this may also have influenced the high CRP level in the group without periodontitis, given that this group not only included healthy individuals but also individuals with mild to moderate periodontal conditions.

It is also emphasized that the individuals' psychosocial characteristics (such as stress, depression or social support) were not evaluated, although it is shown in the literature that individuals under unfavorable psychosocial conditions present elevated inflammatory markers[22].

On the other hand, in the present study, the importance of factors such as body mass index, blood glucose and socioeconomic condition was tested in relation to variability in CRP levels, given that individuals' characteristics should be taken into account with regard to intergroup differences and investigation of causal and non-causal associations. This approach is further justified by the notion that prevention and control measures for cardiovascular diseases should involve not only management of classical risk factors such as smoking, hypertension and obesity but also policies aimed towards improvement of living conditions.

It is known that individuals of low socioeconomic level are more likely to have behavior that is harmful to health, exposure to higher levels of psychological stress and, on average, less information and smaller sources of funds[23].

Although some studies have highlighted that the magnitude of such associations varies according to the socioeconomic stratum, the variable of low socioeconomic level in the present study (as determined by the sampling localities of Monte Gordo and Salvador) was a confounding variable in this relationship. It caused a change to the main predictive variable of the order of 22%, but did not determine the CRP level, probably because of the small size of the subsample with high socioeconomic level.

Although other covariables have classically been known to interfere with the variability of CRP levels, such as hypertension, smoking, age and sex, these were not kept in the final model, given that according to the presuppositions of linear regression analysis, it has been suggested that there should be at least 20 analysis units for each independent variable in the model[24]. Thus, the present study was limited to three independent variables because of the small sample size, so as to avoid overadjustment that might distort the results.

In addition to the abovementioned care regarding the analysis, care was also taken to use criteria for defining periodontal disease that would make it possible to only include individuals with severe periodontitis in the case group. This was done because it has been demonstrated, particularly in prospective studies, that the greater the severity of the periodontitis is, the less the reduction in the inflammatory response monitored by the serum CRP concentrations will be[25].

Although the findings of the present study did not confirm statistical significance for the hypothesis investigated, it is increasingly evident that periodontal disease appears to take on an important role as a risk factor for the appearance of certain systemic diseases, such as pulmonary infections, cardiovascular events, induction of premature delivery and birth of low-weight children[26]. Nonetheless, dental professionals should remain aware that the topic of the influence of periodontal infection on the systemic inflammatory burden is still not an established fact.

From this perspective, it can be suggested that further studies should be conducted, with prospective evaluations, with the aim of clarifying what the real role of CRP is, in the interrelationship between periodontal disease and cardiovascular events.

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