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Is C-Reactive Protein an Indicator of Periodontal Risk?

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Abstract: Periodontitis is a chronic, multifactorial, inflammatory disease caused by microorganisms and characterized by the progressive destruction of tooth-supporting tissue. In recent years, studies have shown a correlation and association between periodontitis and atherosclerotic cardiovascular disease, because both the disease has some similar risk factors and they produce an increase in plasma C-reactive protein (CRP) level. This protein has been attributed favorable characteristics as an inflammatory marker. This study was aimed to identify if there is any relationship between periodontitis and CRP values before starting periodontal treatment in a group of patients from the Faculty of Dentistry of the University of Costa Rica. Periodontal examinations were performed on 30 patients, and a blood sample was obtained from each patient to determine the P-CR concentration. The average P-CR was found to be 3.72mg/L (95%CI: 2.06–5.38), which is a moderate to severe risk marker. Fifty-four percent of the total patients had chronic generalized periodontal disease, with no significant difference between the different periodontal disease with gender (p=0.416) or age (p=0.477). Meanwhile, forty-three and three percent of the total patients had localized chronic periodontal disease, and gingivitis respectively. It was observed that the female gender showed a relatively higher cardiovascular risk compared to the opposite gender (p=0.640). In contrast, no statistically significant difference was found in the P-CR value by gender, age or the presence of other diseases, although it was higher in those with metabolic diseases (5.5mg/L) compared to those without (2.7mg/L).

Keywords: Periodontitis; C-reactive protein; Cardiovascular disease

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1. Introduction

Periodontitis is a chronic, inflammatory disease caused by multiple factors, mainly caused by dental biofilm. The mechanism which caused the damage is the production of pro-inflammatory cells that can damage the bone matrix, which are elevated in the bloodstream [1,2]. Bacteria can invade into the tissues that forms the periodontium, thereby generating an immune response by the host body against the bacteria, however, this response could cause damage to the healthy tissue [1]. Among the established risk factors for periodontal disease, there are some risk factors which are modifiable and related to an individual lifestyle, such as smoking, obesity, type II diabetes, stress, and diet. In addition, the incident of overweight and obesity are increasing in recent years, and become a global public health problem. Several studies have shown a higher prevalence or severity of periodontitis incident in the overweight or obese individuals compared to non-overweight individuals [3]. The difference in the internal environment between these two groups may contribute to this observation, for example, there are some differences in the oral microbiota content

between the overweight or obese individuals and non- non-overweight individuals [4]. More research is conducted with the aim to find the link between individuals with obesity and increased level of inflammatory response. Further, the increase in inflammatory mediators is thought to be produced by the adipose tissues [5].

In addition, some studies have linked some clinical manifestations of cardiovascular disease (such as myocardial infarction, stroke, angina or sudden death) to the inflammatory alterations produced by periodontitis [6,7].

The inflammatory aspect of these two conditions can be justified by the similarity in the pathogenic, clinical, and pathophysiological features [8]. Both the conditions are linked to the systemic effects of bacterial lipopolysaccharides released at the site of periodontal infection, subsequently travel through the bloodstream and can anchor in the sub-endothelium of the intima, leading to overexposure of adhesion molecules by the endothelial cells. This binding leads to the detection of proinflammatory proteins such as proinflammatory cytokines or some other substances such as C-reactive protein found in plasma [9]. C-reactive protein is an accurate biomarker used in the inflammatory and infectious processes, interestingly, the American Heart Association included the increase in the C-reactive protein level as a cardiovascular risk factor.

C-reactive protein is a plasma protein involved in the acute phase response, a phenomenon involving non-specific biochemical changes in response to inflammatory and infectious processes, malignancies or tissue damage [10]. Further, the liver is the major site for the synthesis and secretion of this protein, and its production is increased in response to interleukin stimulus [11].

In most countries, the prevalence of periodontitis is estimated to be greater than 50% [12]. Meanwhile, in a study conducted in Costa Rica, the prevalence of periodontal disease was found to be 35%, with a prevalence of 59.10% and 40.64% in the age group 20-45 years and age group 64 years and older respectively [13].

Globally, cardiovascular diseases are the leading cause of death, and in Costa Rica the figures are very similar. According to the National Institute of Statistics and Censuses (NISC) report, of the 11,000 deaths registered in the first half of 2020, 573 death cases were due to acute myocardial infarction, while more than 1, 200 death cases are reported due to heart-related and cerebrovascular diseases.

Given the high incidence of patients suffering from both the diseases and there is a correlation between both the diseases, therefore this study was conducted with the aim of finding the concentration of C-reactive protein in a group of patients who come for periodontal treatment to the Preclinic of Periodontology of the University of Costa Rica. Knowledge of these values will relate the blood findings to the extent of periodontal disease and whether there are other inflammatory diseases that may be associated.

2. Materials and methods

This study was conducted in 30 patients who attended the Faculty of Dentistry of the University of Costa Rica to receive the periodontal treatment. The informed consent form was approved by the Scientific Ethical Committee of the University of Costa Rica in session No.260 on October 9, 2013, and the form was signed by the patients prior to participation in this study. Participants were selected based on the following inclusion and exclusion criteria.

Inclusion criteria:

(1) Individuals over 18 years of age.
(2) Individuals with clinical diagnosis of chronic periodontitis.
(3) Individuals with at least 20 teeth in the mouth

Exclusion criteria:

(1) Individuals who have started the periodontal treatment within the last 6 months.
(2) Individuals who have received antibiotic therapy 6 months before starting the treatment
(3) Women who are pregnant or breastfeeding

All patients underwent a health questionnaire and were asked if they suffered from any chronic diseases such as diabetes or hypertension. A periapical radiographic examination was performed with a parallel technique, periodontal probing was performed in six sites per tooth, the degree of mobility, and the indices of bleeding and dental plaque were established. All this test was performed in the Periodontics Preclinic, reviewed, and endorsed by the section instructors. With the information obtained, a periodontal diagnosis was made for each patient.

Before starting the treatment, a blood sample was obtained from each participant. The collected blood samples were analyzed using the quantitative determination of hs-CRP (high-sensitivity C-reactive protein) in serum on the Roche/Hitachi cobas c111 systems. Measurements of P-CR concentrations were performed at the Centre for Research in Cellular and Molecular Biology of the UCR (CRCMB).

3. Results

The medical, dental, and periodontal condition of 30 patients was analyzed. A convenience coding was established for each variable; categorizing gender as 0 for men and 1 for women; periodontal diagnosis as 0 for gingivitis, 1 for localized chronic periodontitis and 2 for generalized chronic periodontitis; associated metabolic diseases as 0 for those without systemic involvement, 1 for diabetes mellitus, 2 for arterial hypertension, 3 for rheumatoid arthritis and 4 for other pathologies. In addition, the age in years of each patient and the P-CR value (mg/L) obtained from the laboratory examination was included. A summary of the findings is presented in **Table 1**.

Table 1. Coded data of the subjects participating in the study, according to gender, age, periodontal diagnosis, C–reactive protein (CRP) value and the presence of associated metabolic diseases (UCR, J. Castillo).

No.	Gender	Age (Years)	Periodontal diagnosis	P–CR value (mg/L)	Associated diseases
1	0	43	1	7.81	0
2	1	57	2	5.35	1
3	1	47	2	12.55	4
4	0	55	1	20.35	4
5	1	29	2	5.33	0
6	1	51	2	3.63	0
7	1	66	1	5.2	3
8	1	58	1	1.18	2
9	0	42	2	2.07	0
10	0	63	2	0.84	0
11	0	33	2	0.57	0
12	0	34	1	1.89	0
13	0	47	2	0.95	0
14	0	40	2	0.71	4
15	0	21	2	0.43	0
16	1	32	0	0.60	0

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No.	Gender	Age (Years)	Periodontal diagnosis	P–CR value (mg/L)	Associated diseases
17	1	31	1	1.28	0
18	0	23	1	0.51	0
19	0	35	2	1.05	0
20	0	59	2	1.49	4
21	0	29	1	2.1	0
22	1	42	2	2.02	0
23	0	54	2	0.63	0
24	1	23	1	1.25	0
25	1	55	2	2.37	4
26	0	51	1	1.05	4
27	0	40	2	9.50	0
28	0	37	1	9.25	0
29	1	27	1	4.29	4
30	0	46	1	5.42	4

Based on **Table 1**, the mean age was 42.7 years (95%CI: 38.2-42.7), of which 40% were female. Although no statistically significant difference was found in the mean age of females compared to males, it was observed that the female gender had a higher P-CR concentration value compared to the male gender.

Table 2 summarizes the results of the age groups with the highest cardiovascular risk according to P-CR levels. The range with the highest cardiovascular risk ranged from 40-49 years.

Table 2. Patients were classified according to a ten-year age group by cardiovascular disease risk (UCR, J. Castillo)

Ten-year age groups	Low Risk		Medium Risk		High Risk	
(years)	#	%	#	%	#	%
20–29	2	40%	2	40%	1	20%
30–39	2	28.5%	3	42.8%	2	28.5%
40–49	2	25%	2	25%	4	50%
50–59	1	12.5%	4	50%	3	37.5%
60 and above	1	50%	0	0%	1	50%

Figure 1 presents the percentage of distribution of the participants' metabolic conditions. 36% of the patients had chronic metabolic diseases, such as type 2 diabetes mellitus, hypertension or rheumatoid arthritis.

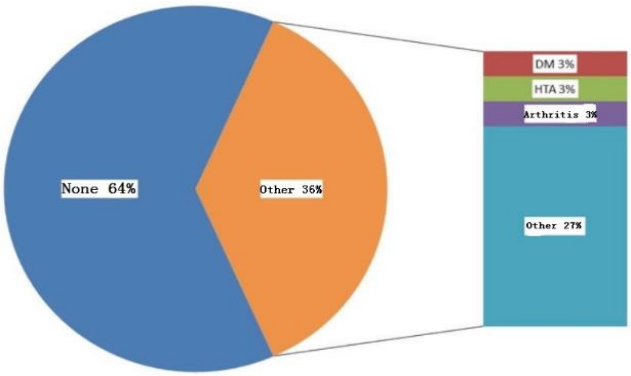

Figure 1. Distribution of patients according to disease prevalence (UCR J. Castillo)

Regarding periodontal diseases, 3% of the patients had gingivitis, 43% had localized chronic periodontal disease, and 54% had generalized chronic periodontal disease, with no statistically significant difference by gender (p=0.416) or age (p=0.477).

Regarding the P-CR value, the average was found to be 3.72mg/L (95%CI: 2.06–5.38) (MODERATE TO HIGH RISK). Although no statistically significant difference was found in P-CR values by sex, age or the presence of other metabolic diseases, the average was higher for those with disease (5.5mg/L) compared to those without (2.7mg/L). These data are shown in **Figure 2**.

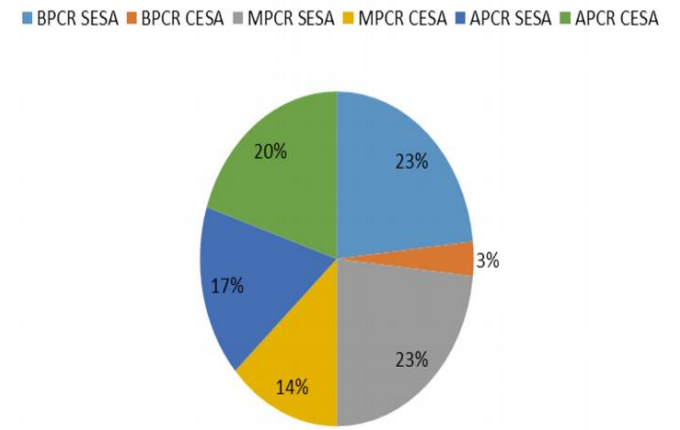

Figure 2. Percentage distribution of patients, according to P-CR content and the existence of associated systemic diseases (UCR, J. Castillo). Note: BPCR SESA=Low P–CR content (<1mg/L) and no associated systemic disease; BPCR CESA=Low content of P–CR content (<of 1mg/L) and with the existence of associated systemic disease; MPCR SESA=Medium content of P–CR (from 1 to 3mg/L) and no associated systemic disease; MPCR CESA=Medium content of P–CR content (from 1 to 3mg/L) and with the existence of associated systemic disease; APCR SESA=High P–CR content (≥ 3mg/L) and no associated systemic disease. APCR CESA=High P–CR content (≥ 3mg/L) and with associated systemic disease.

Although no statistically significant differences were found by periodontal diagnosis, gender, age or the presence of other comorbidities, those who reported having chronic diseases had higher P-CR values. Of all the patients, 26% showed low levels (less than 1mg/L), 37% showed medium levels (1–3mg/L) and 37% showed higher levels (more than 3mg/L). These values are related to patients who did not report any metabolic condition.

4. Discussion

Differences related to gender and age were not significant. According to published research [10], serum

levels have been found to be slightly higher in women than in men, which is consistent with the results obtained in the present study.

The age range with the highest cardiovascular risk was 40-49 years. A linear behavior is observed with respect to the age range and cardiovascular risk, according to the observed P-CR values. Some studies have shown that the average concentration of P-CR in healthy blood donors is 0.8mg/L, but when stimulated the level of P-CR can increase its production more than ten thousand times [10]. The same researchers concluded that the serum levels of P-CR tend to increase with age with an increase in the frequency of subclinical inflammatory processes and the number of apoptotic phenomena.

With respect to systemic condition and gender, this study showed no relevant differences, this may also be affected by the small sample size. Despite the above, the results showed that 50% of all female subjects had associated systemic diseases such as hypertension, diabetes mellitus, rheumatoid arthritis or asthma. Of the male subjects, the percentage of patients with associated systemic diseases was lower (33%) compared to the opposite gender.

In the case of cardiovascular disease, especially atherosclerotic disease, its impacts differ according to sex, regardless of whether individuals have the same prevalence of coronary risk factors [14]. The deleterious effect manifests itself later in women as seen in acute myocardial infarction, whose average age of presentation is 10 years later than in men. Therefore, the male gender is more prone to present cardiovascular alterations and to manifest them at a younger age compared to the female gender. This characteristic is shared by cerebrovascular disease (CVD) and periodontal disease.

With regard to P-CR levels, a mean of 3.72mg/L was obtained, which is within the high-risk range for cardiovascular disease. According to the sources consulted, high-sensitivity P-CR (hs-CRP) is cited as an accepted inflammatory marker as a predictor of cardiovascular risk [15]. The same authors suggested that, based on the publication of the American Heart Association and the Center for Disease Control, (USA, since 2003), plasma hs-CRP concentrations below 1mg/L is considered a low CVD risk, whereas, concentrations fluctuating between 1–3mg/L is considered a medium risk. On the other hand, concentrations above 3mg/L are associated with an increased risk of developing cardiovascular disease and values above 3mg/L are used to define individuals at high cardiovascular risk.

The P-CR values found were not significant in respect to age, sex or periodontal diagnosis. However, the behavior of P-CR in relation to the presence of systemic involvement shows that P-CR levels increase more in these patients in particular.

According, to **Figure 2** on the percentage distribution of P-CR level and the existence of associated diseases, the differences between the high, medium and low risk groups, as mentioned above, were not significant.

According to the same figure, the total sample with both low and medium levels of P-CR, the highest percentage of the sample was represented by patients without associated systemic diseases. This situation varied in the group with high P-CR levels, where out of the total of 37%, a higher percentage of patients with high P-CR levels (above 3mg/L) and associated systemic diseases (20%) was observed, compared to the group of patients with high P-CR levels without associated systemic diseases.

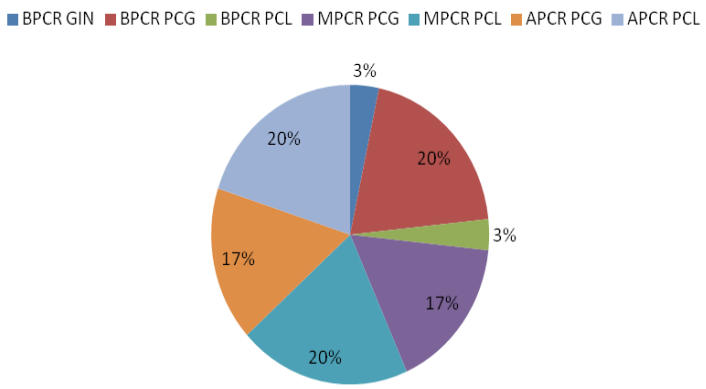

Figure 3. Percentage distribution of patients, according to P-CR content and periodontal diagnosis (UCR, J. Castillo). Note: BPCR GIN=Low P-CR levels (< 1mg/L) and gingivitis; BPCR PCG=Low P-CR levels (< 1mg/L); BPCR PCL=Low P-CR content (< 1mg/L) and localized chronic periodontitis; MPCR PCG=Medium P-CR content (1 to 3mg/L) and chronic generalized periodontitis; MPCR PCL=Medium P-CR content (1 to 3mg/L) and localized chronic periodontitis; APCR PCG=High P-CR content (≥ 3 mg/L) and chronic generalized periodontitis; APCR PCL=High P-CR content (≥ 3 mg/L); and localized chronic periodontitis.

These results are comparable with another published research [16]. The author observed that some individuals with periodontal disease had altered P-CR levels, however, not all individuals with periodontitis has an altered P-CR level. This was similar in this study, where 6 of the 16 subjects diagnosed with chronic generalized periodontitis (37.5%) had values considered to be at low cardiovascular risk, being below 1mg/L of P-CR in blood. The same authors Cite Beck and Offenbacher, who justify this behavior on the basis of genetic evidence, as some people have a hyperinflammatory phenotype, responding in an exaggerated manner to an inflammatory stimulus, such as, periodontal disease.

Periodontitis, like any other disease, is capable of promoting inflammation [17], further lead to increase in the P-CR levels [18]. As a result of the correlation between high P-CR levels and periodontal disease, the study did not show any significant relationship.

5. Conclusion

The results of P-CR levels showed a mean value of 3.72mg/L, equivalent to a high risk of cardiovascular disease. There was no statistically significant relationship between P-CR values and sex, age, metabolic diseases and periodontal condition. The highest PC-R values were found in some patients with no history of metabolic diseases.

Disclosure statement

The authors declare no conflict of interest.

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