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CLINICAL RESEARCH:

# Effects of Periodontal Treatment on CRP and Other Cellular Markers in Blood

## Efecto del tratamiento periodontal en la PCR y otros marcadores celulares en sangre

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ABSTRACT: Periodontitis is a chronic inflammatory disease that affects public health worldwide. It has been related to microorganisms that trigger an inflammatory response that, in turn, produces a deterioration of the teeth's supporting tissue. In recent years, studies have shown some similarity and association between periodontitis and atherosclerotic cardiovascular disease. The serum increases in C-reactive protein (CRP), fibrinogen, alpha-1 antitrypsin, moderate increase in leukocytes, increase in sedimentation rate and Von Willebrand factor antigen make it likely that there is a relationship between periodontal disease and other systemic conditions, specifically atherosclerotic disease. This study seeks to establish if there is any relationship between these values after phase II periodontal treatment in patients with periodontitis at the Faculty of Dentistry of the University of Costa Rica. The initial values are found in a previous publication (1). In this second stage, the sample was reduced to 14 patients, of whom 57% presented metabolic compromise such as rheumatoid arthritis, arterial hypertension and diabetes mellitus, and 50% decreased PCR levels. As for the mean level of the total sample, in both stages of the study, PCR increased from 2.72 (SD: 2.25) to 5.36 (SD: 9.68). Of the patients who received periodontal treatment, 21.4% had low PCR levels (<1 mg/L), 50% medium (1-3 mg/L) and 28.6% high (>3 mg/L). There was no statistically significant difference in any of the variables analyzed for cholesterol, triglycerides and fibrinogen. Of the total number of patients in whom carotid ultrasound was performed, 52.4% were diagnosed as healthy, 33.3% had bulbar myointimal hyperplasia and 14.3% had atheromatous plaques. One of the participants died of myocardial infarction. This study does not conclude that there is a relationship between periodontal disease and cellular markers, which are also found in atheromatous disease, but it can be affirmed that there is a probability that periodontal disease contributes to affect the metabolic condition of the patient.

KEYWORDS: Periodontitis; Cardiovascular disease; Atherosclerosis; Inflammation; C-reactive protein.

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RESUMEN: La periodontitis es una enfermedad inflamatoria crónica que afecta la salud pública a nivel mundial. Ha sido relacionada con microorganismos que desencadenan una respuesta inflamatoria que, a su vez, produce un deterioro del tejido de soporte de los dientes. En los últimos años, se han realizado estudios que señalan cierta similitud y asociación entre la periodontitis y la enfermedad cardiovascular aterosclerótica. El aumento sérico de la proteína C reactiva (PCR), el fibrinógeno, la alfa-1 antitripsina, el aumento moderado de leucocitos, el incremento en la velocidad de sedimentación y del antígeno del factor de Von Willebrand hacen probable que exista relación entre la enfermedad periodontal y otros padecimientos sistémicos, específicamente la aterosclerótica. Este estudio busca establecer si existe algún tipo de relación entre estos valores después del tratamiento periodontal de fase II en pacientes con periodontitis de la Facultad de Odontología de la Universidad de Costa Rica. Los valores iniciales se encuentran en una publicación previa (1). En esta segunda etapa, la muestra se redujo a 14 pacientes, de los cuales el 57 % presentó compromiso metabólico como artritis reumatoidea, HTA y diabetes mellitus, y el 50 % disminuyó los niveles de PCR. En cuanto al nivel promedio de la muestra total, en ambas etapas del estudio, la PCR aumentó de 2,72 (DS: 2,25) a 5,36 (DS: 9,68). El 21,4 % de los pacientes que recibieron el tratamiento periodontal presentó niveles bajos de PCR (< a 1 mg/L), un 50 % medios (1-3 mg/L) y el otro 28,6 % elevados (> a 3 mg/L). No hubo una diferencia estadísticamente significativa en ninguna de las variables analizadas en función de colesterol, triglicéridos y fibrinógeno. Del total de pacientes en los que se realizó el ultrasonido de carótidas, el 52,4 % fue diagnosticado como sano, el 33,3 % presentó hiperplasia miointimal bulbar y el 14,3 % placas ateromatosas. Uno de los participantes falleció de un infarto del miocardio. Este estudio no concluye que haya una relación entre la enfermedad periodontal y marcadores celulares, que también se encuentran en la enfermedad ateromatosa, pero si se puede afirmar que existe una probabilidad de que la periodontal contribuya a afectar la condición metabólica del paciente.

PALABRAS CLAVE: Periodontitis; Enfermedad cardiovascular; Aterosclerosis; Inflamación; Proteína C reactiva.

## INTRODUCTION

Periodontitis is a chronic inflammatory disease caused by multiple factors, but mainly by dental biofilm (2). Among the established risk factors for periodontal disease, there are some that are modifiable and related to the person's lifestyle, such as smoking, obesity, type II diabetes, stress and diet (3). Specifically, with regards to overweight and obesity, it is known that they currently constitute a worldwide public health problem that has been increasing in recent years (4). Several studies show a higher prevalence or severity of periodontitis in overweight or obese individuals when compared to non-overweight people (5, 6). This is due to several differences in these populations (7). For example, differences have been found in the oral microbiota of obese and non-obese individuals (8). Research is trying to find the relationship of individuals with obesity to have an increased inflammatory response. It is believed that this increase in inflammatory mediators is produced by adipose tissue (9).

Several studies have related some clinical manifestations of cardiovascular disease (myocardial infarction, stroke, angina or sudden death) to the inflammatory alterations produced by periodontitis (10, 11).

The inflammatory aspect presented by these two disorders may be justified by the similarity of

pathogenic, clinical and pathophysiological features (12), both linked to the systemic effects of bacterial lipopolysaccharides released at the site of periodontal infection, which travel through the bloodstream and can anchor in the subendothelium of the intima, generating an overexposure of adhesion molecules by endothelial cells (13). This binding leads to the detection of proinflammatory cells such as cytokines of this type or some other substances such as C-reactive protein, which is found in plasma (14) and constitutes an accurate marker in inflammatory and infectious processes, so much so that the American Heart Association of the United States lists it as a cardiovascular risk factor (15).

C-reactive protein is a plasma protein involved in the acute phase response, a phenomenon that involves non-specific biochemical changes in response to inflammatory and infectious processes, malignant neoplasms or tissue damage (16).

The liver is the site of major synthesis and secretion of this protein. Its production is increased when there is an interleukin stimulus (16).

In most countries, it is estimated that the prevalence of periodontitis is greater than 50% (17), however, in a study conducted in Costa Rica, it was determined to be 35%, where the age group between 20 and 45 years presented a predominance of 59.10% and 40.64% in the group of 64 years and older (18).

Cardiovascular diseases are the leading cause of death in the world and in Costa Rica the figures are very similar. According to the National Institute of Statistics and Census (INEC), of the 11,000 deaths registered in the first half of 2020, 573 corresponded to acute myocardial infarction and more than 1,200 to heart-related and cerebrovascular diseases (19).

Given the high incidence of patients suffering from both diseases and the relationship that has been established between them, it was decided to carry out this study in order to determine the concentration of C-reactive protein and other proinflammatory markers in a group of patients who received periodontal treatment at the Preclinic of Periodontics of the University of Costa Rica. They underwent complete blood counts, blood lipid tests (to analyze cholesterol and triglyceride values) and to determine fibrinogen levels. At the Calderón Guardia hospital, a triplex carotid ultrasound was performed to look for atheromatous plaques. 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.

## MATERIALS AND METHODS

The second part of the study was carried out with 14 patients who attended the Faculty of Dentistry of the University of Costa Rica (of the 30 who started the study) and who received periodontal treatment. The participants signed the Informed Consent form, approved by the Scientific Ethical Committee of the University of Costa Rica in session No. 260 of October 9, 2013, and met the following inclusion and exclusion criteria.

### INCLUSION CRITERIA

To have been previously selected to participate in the study.

### EXCLUSION CRITERIA

To have started antibiotic therapy after the treatment was performed.

For this second part of the study, these patients received follow up; however, 16 of the 30

who started decided not to continue for personal reasons (lack of interest, acceptable oral health condition or other reason).

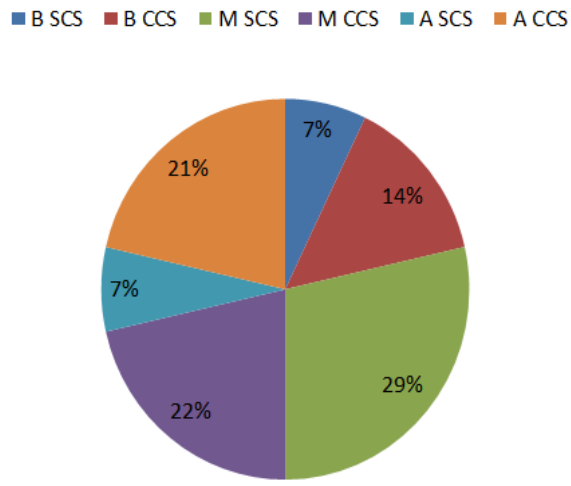
The participants in this second stage had already been diagnosed with periodontal disease or gingivitis. All participants completed the periodontal hygiene phase treatment, including supragingival and subgingival instrumentation and dental biofilm control. Blood tests were performed between one and three months after completion of periodontal treatment.

## RESULTS

The medical, dental and periodontal condition of 14 patients after periodontal treatment was analyzed, as well as a complete blood examination, assessment of PCR and fibrinogen levels, in addition to a carotid ultrasound. To analyze the information, the study variables were coded.

The mean age for the second stage was 50.6 years (IC 95%: 43, 8-57, 5), of which 64.3% were men and 35.7% women. No statistically significant difference was found in the mean age of women with respect to men (p=0.833).

The most common diseases found were arterial hypertension with 42.8% and rheumatoid arthritis with 7.1%, which occurred in isolation or combined with other conditions such as diabetes mellitus, dyslipidemias, hypothyroidism and obesity. Forty-three percent of patients did not suffer from metabolic diseases (Figure 1).




B SCS= Low P-CR content (< 1 mg/L) and no systemic compromise.
B CCS= Low P-CR content (< 1 mg/L) and with systemic compromise.
M SCS= Medium P-CR content (1 to 3 mg/L) and no systemic compromise.
M CCS= Medium P-CR content (1 to 3 mg/L) and with systemic compromise.
A SCS= Medium P-CR content (≥ 3 mg/L) and no systemic compromise.
A CCS= Medium P-CR content (≥ 3 mg/L) and no systemic compromise.

**Figure 1**. Percentage distribution of patients according to CRP content and the existence of associated systemic diseases after Phase I periodontal treatment (UCR, 2014).

Regarding periodontal condition, 71% of the patients presented generalized chronic periodontitis and 29% localized chronic periodontitis, with no statistically significant difference by sex (p=0.052) or age (p=0.563).

After phase 2 of periodontal treatment, 21.4% of the patients had low PCR levels (< 1 mg/L), 50% had medium levels (1-3 mg/L) and 28.6% had high levels (> 3 mg/L). For those who showed both low and high PCR levels, the highest percentage was represented by patients with associated systemic diseases. This result varied in the group with mean

PCR levels, where a higher percentage was observed in those without systemic diseases (Figure 2).

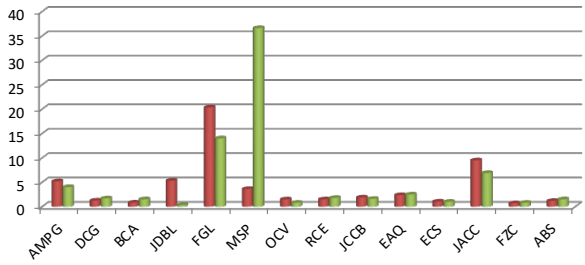



**Figure 2**. Comparison of C-reactive protein value before (red) and after (green) periodontal treatment (UCR, 2014).

The parameters of total cholesterol, HDL cholesterol and LDL cholesterol had a decrease in the second part of the study. However, the cardiovascular risk indicator (Castelli index = total cholesterol/HDL cholesterol ratio) increased from 4.46 (SD: 1.00) to 4.94 (SD: 2.14), so it can be stated that most patients show a tendency to double cardiovascular risk. The total cholesterol level, despite the decrease mentioned above, was always found to be elevated with respect to normal.

Triglyceride levels increased for the second part of the investigation but remained within the normal range.

Fibrinogen remained within normal limits; however, it increased in the 14 patients of the study from 323.42 (SD: 88.48) to 329.92 (SD: 98.48).

The mean PCR level increased in the second part from 2.72 (SD: 2.25) to 5.36 (IC 95%: 0.0-10.9). No statistically significant difference was found in the PCR value by sex (p=0.351) or age (p=0.423).

All the variables studied before and after periodontal treatment in the 14 patients did not show statistically significant differences in any of them.

Of the 12 patients who underwent carotid ultrasound and participated in both parts of the study, 52.4% were diagnosed as healthy, 33.3% with bulbar myointimal hyperplasia and 14.3% with atheromatous plaques in the carotids.

## DISCUSSION

Differences related to gender and age were not significant. According to research, slightly higher serum levels have been detected in women than in men, data consistent with the results of the present study (20).

The age range with the highest cardiovascular risk was that which included subjects between 40 and 49 years of age. Linear behavior was observed with respect to age range and cardiovascular risk, according to the PCR values obtained. Some studies have shown that the average concentration of PCR in healthy blood donors is 0.8 mg/L, but, in response to a stimulus, its production can increase more than ten thousand times (21). The same researchers concluded that serum PCR levels tend to rise with age, and this is related to 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, in the data obtained, it was observed that 50% of the total female subjects suffer from associated systemic diseases such as arterial hypertension, diabetes mellitus, rheumatoid arthritis or asthma, while, of the total male gender, the percentage of patients with associated systemic diseases was lower (33%) compared to the opposite gender (22).

In the case of cardiovascular disease, especially atherosclerotic disease, it has a different impact according to sex, regardless of whether individuals have the same prevalence of coronary

risk factors (23). 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 (24). Therefore, men are more prone to present cardiovascular alterations and to manifest them at a younger age than women. This characteristic is shared by cerebrovascular disease (CVD) and periodontal disease (24).

With respect to PCR levels, a mean of 3.72 mg/L was obtained, a value that is within the high-risk range for cardiovascular disease. According to the sources consulted, high-sensitivity PCR (hs-PCR) is cited as an inflammatory marker accepted as a predictor of cardiovascular risk (25). The same authors suggest that, based on a 2003 publication by the American Heart Association and the Center for Disease Control, plasma hs- PCR concentrations below 1 mg/L are considered low CVD risk, whereas those fluctuating between 1 and 3 mg/L are considered medium.

On the other hand, concentrations greater than 3 mg/L are associated with an increased risk of developing cardiovascular disease, and values above this define individuals at high cardiovascular risk (25).

The PCR values found showed no relevance with respect to age, sex or periodontal diagnosis. However, the behavior of PCR in relation to the presence of systemic compromise shows that PCR levels increase more in these patients in particular.

Of the whole sample, for those who presented both low and medium PCR levels, the highest percentage of the sample was represented by patients without associated systemic diseases. However, this situation varied in the group with high levels where, of the total of 37%, a higher percentage (above 3 mg/L) and associated systemic diseases (20%) were observed, this with respect to the group of patients with high PCR levels without associated systemic diseases.

These results are comparable with those achieved by other investigators (26), who observed that PCR levels were altered only in some individuals with periodontal disease and not in all those with periodontitis (27). This happened similarly in this study, where 6 of the 16 subjects diagnosed with chronic generalized periodontitis (37.5%) presented values considered to be of low cardiovascular risk, below 1 mg/L of PCR in blood (28). This behavior is justified on the basis of genetic evidence, since some individuals present a hyperinflammatory phenotype, responding in an exaggerated manner to an inflammatory stimulus such as periodontal disease.

Periodontitis, as well as any other disease, is capable of promoting an inflammatory crisis, which causes an increase in PCR levels (29).

As a result of the correlation between high PCR levels and periodontal disease, the study did not show a significant relationship.

## CONCLUSIONS

The results of PCR levels showed a mean value of 3.72 mg/L, equivalent to a high risk of cardiovascular disease.

There was no statistically significant relationship between PCR values and sex, age, metabolic diseases and periodontal condition.

The highest PCR values were found in some patients, without any history of metabolic diseases.

The quantification of PCR value is a suggested molecular analysis for any medical-dental procedure, (emphasis on periodontal therapy), to

determine the cardiovascular risk before initiating any type of treatment.

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