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Association between periodontal disease and systemic inflammation in patients on chronic hemodialysis.

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Key words: periodontal disease; hemodialysis; inflammation; chronic kidney disease.

Abstract. Previous studies have demonstrated that severe chronic periodontitis is associated with an increased risk of cardiovascular mortality in the hemodialysis population. However, the association between periodontal disease and systemic inflammation in these patients is not yet fully understood. C - reactive protein (CRP) is one of the plasma proteins that appear in the acute phase of inflammation. Periodontitis is associated with elevated levels of CRP in adults and with its decrease after treatment. The aim of this study was to evaluate the association between periodontal disease and systemic inflammation in patients on chronic hemodialysis (HD). An analytical cross-sectional study was carried out on 111 outpatients with end-stage renal disease (ESRD) on chronic HD. Periodontal disease was measured by periodontal pocket depth (PPD), loss of clinical attachment level (CAL), gingival index, and plaque index. Systemic inflammation was measured by high-sensitivity C-reactive protein (hs-CRP) levels. A multivariable linear regression model was created using hs-CRP as the dependent variable. Eighty-four patients with low hs-CRP levels (≤1 mg/dL) and 27 patients with high hs-CRP levels (>1 mg/dL) were included. Patients with high hs-CRP were older, with diabetes, and with higher scores in oral health indexes. hs- CRP levels had a significant positive correlation with age, gingival index, PPD, and loss of clinical-attachment level. Finally, regression identified PPD and diabetes as independent hs-CRP contributors. In patients on chronic HD, PPD is an independent contributor of systemic inflammation.

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Asociación entre enfermedad periodontal e inflamación sistémica en pacientes en hemodiálisis crónica.

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Palabras clave: enfermedad periodontal; hemodiálisis; inflamación; enfermedad renal crónica.

Resumen. Estudios anteriores han demostrado que la periodontitis crónica grave se asocia con un mayor riesgo de mortalidad cardiovascular en la población en hemodiálisis. Sin embargo, la asociación entre la enfermedad periodontal y la inflamación sistémica en estos pacientes aún no se conoce completamente. La proteína C-reactiva (PCR) es una de las proteínas plasmáticas que aparecen en la fase aguda de la inflamación. La periodontitis se asocia con niveles elevados de PCR en adultos y con su disminución después del tratamiento. El objetivo del estudio fue evaluar la asociación entre la enfermedad periodontal y la inflamación sistémica en pacientes con hemodiálisis crónica. Se realizó un estudio analítico de corte transversal en 111 pacientes ambulatorios con enfermedad renal en etapa terminal en hemodiálisis crónica. La enfermedad periodontal se midió por profundidad de bolsa periodontal (PBP), pérdida del nivel de inserción (PNI), índice gingival e índice de placa. La inflamación sistémica se midió por niveles de proteína C-reactiva de alta sensibilidad (PCR-as). Se creó un modelo de regresión lineal multivariado utilizando PCR-as como variable dependiente. Se incluyeron 84 pacientes con bajos niveles de PCR-as (≤1 mg/dL) y 27 pacientes con niveles altos de PCR-as (>1 mg/dL). Los pacientes con PCR alta fueron mayores, con diabetes y con mayores puntajes en los índices de salud oral. Los niveles de PCR-as tuvieron una correlación positiva significativa con la edad, el índice gingival, la PBP y la PNI. Finalmente, la regresión identificó PBP y diabetes como colaboradores independientes de PCR-as. En pacientes con hemodiálisis crónica, la PBP contribuye de manera independiente a la inflamación sistémica.

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INTRODUCTION

Patients with chronic kidney disease (CKD) experience a significant increase in the rate of atherosclerotic complications. Coronary heart disease and cerebrovascular disease complications remain the leading causes of death in patients on chronic hemodialysis (HD) (1). Because traditional risk factors did not completely explain this high risk, the understanding of different non-traditional predictors of mortality could improve the patients' treatment and increase their survival (2). Chronic inflammation, characterized by increased C-reactive protein (CRP) levels, has been associated with cardiovascular death in both general population and in patients on HD (3-5).

Periodontal disease (PD) is a chronic infection of tooth-supporting structures caused primarily by Gram-negative anaerobes. This process is initiated in the gingiva, if untreated; it leads to alveolar bone destruction and eventually, tooth loss (6). In susceptible individuals, microorganisms can evade local defenses and invade the bloodstream, inducing a systemic inflammatory response that includes elevation of CRP (7).

Previous studies have demonstrated that severe chronic periodontitis is associated with an increased risk of cardiovascular mortality in the population with end-stage renal disease (ESRD) (8). PD has been associated with risk of CKD and consequently periodontitis may be a covert, but treatable source of systemic inflammation in the end-stage renal disease population (9). It have been suggested that elevated levels of IgG antibody to bacterial species associated with destructive periodontal diseases are associated with elevated CRP values in HD populations (10). In addition, previous studies have demonstrated that the levels of TNF-α and IL-8 in gingival crevicular fluid was significantly higher in HD patients than in controls.

There was a strong positive correlation between clinical periodontal parameters and the levels of inflammatory cytokines in gingival crevicular fluid in those patients (11). However, the association between periodontal disease and systemic inflammation in patients on HD is not completely understood (12,13), and contradictory results may arise from various, not evaluated, confounders, such as age, gender, diabetes mellitus, and smoking. The possible pathophysiological mechanism by which this process occurs is related to the immune response of the host to the microorganisms that produce toxins. These endotoxins stimulate the defense cells of the periodontal tissues to express different inflammatory mediators, among which are interleukin 1 (IL-1), tumor necrosis factor alpha (TNF-α) or receptor activator of κβ ligand factor (RANKL) (14). In addition, other substances are also released, such as heat shock proteins (HSP60) and CRP (15). These inflammatory mediators may enter the bloodstream and activate liver acute phase proteins, which further amplify systemic inflammation levels (7,16). In blood, the half-life of the CRP is relatively short; however, when there is an acute inflammatory process or a bacterial infection, the plasma concentration increases considerably (17). CRP production is not specific to a disease, but its levels are higher the greater the inflammation and tissue destruction. It has been proposed that CRP may be a possible mediator of the association between periodontitis and inflammatory systemic diseases (18).

The aim of the study was to evaluate the association between periodontal disease and systemic inflammation in patients on chronic HD. The main hypothesis was that there is an association between periodontal pocket depth (PPD) –a marker of active periodontal damage– and the level of CRP –a marker of systemic inflammation.

MATERIAL AND METHODS

An analytical cross-sectional study was conducted at the Nephrology Department of the Hospital Central "Dr. Ignacio Morones Prieto" at San Luis Potosí City, SLP, Mexico. One hundred eleven patients included in this study were diagnosed as cases of ESRD on HD (minimum, 3 months) and were recruited from a public hospital without distinction of age, gender, social level or rural/urban area. All of them came from a low-socio-economic level. The majority of patients had a permanent central catheter; for this reason, this variable was not considered in the analysis. Exclusion criteria comprised being an inpatient, or having an autoimmune disease, cancer and chronic or acute infections. Each

participant was provided with a written informed consent and all procedures were approved by the Hospital Bioethics Committee (registry no. 30-14).

A patient interview was performed during an HD session, in which the most important sociodemographic and clinical data in each patient was recorded. Prior to initiating HD, a venous blood sample from all patients participating in the study was obtained, and a high sensitivity C-reactive protein (hs-CRP) measure was performed using the MULTIGENT CRP Vario™ assay (Archi-Tech cSystems Assay; Abbott Laboratories) (19).

Periodontal evaluation was conducted by a calibrated observer through a one-full-mouth periodontal examination. Oral health indicators were as follows: plaque index (20), measurement of oral hygiene; gingival index (21), measurement of the degree of gingivitis; loss of Clinical Attachment Level (CAL), which indicates cumulative periodontal damage, and finally, periodontal pocket depth (PPD) as a marker of active periodontal damage. All indicators were measured at six points on each tooth. Patients were classified by CAL: normal oral status/mild periodontitis (CAL <4 mm); moderate periodontitis (CAL 4-5.9 mm), and severe periodontitis (CAL ≥6 mm), as previously described (13).

Prior to the study, oral health indicators were repeated by two periodontists in 10 outpatients (207 teeth) to assess inter-observer agreement. The Linn concordance correlation coefficient was 0.90 for gingival index, 0.92 for plaque index, 0.92 for PPD, and 0.95 for CAL.

Descriptive statistics was performed: continuous variables are presented as mean (±Standard Deviation [SD]) and categorical variables as frequency (%). Patients were divided into two groups: those with low hs-CRP levels (<1 mg/dL), and those with elevated hs-CRP levels (>1 mg/dL). Differences between groups were analyzed by the Chi-square test for categorical variables and the Student t test for continuous variables. Correlation between hs-CRP and other variables were tested using Spearman Rho test. A multiple linear regression model was created using hs-CRP as dependent variable, with log transformation for non-normal variables. Curved linear relationships of covariables were evaluated, and then quadratic terms were added, if appropriate. Also, the model was tested for multicollinearity. Statistical analysis was performed using R ver. 3.1.1 for Windows statistical software. A value of $p<0.05$ was considered statistically significant.

RESULTS

Sixty-three patients with normal oral status/mild periodontitis, 22 patients with moderate periodontitis, and 26 patients with severe periodontitis were analyzed. Average age of study population was 42.9 years (±17.8 years), with a mean time on HD of 27.1 months (±30.5 months), 57 (51.3%) of patients were males, and 51 (45.9%) had diabetes. Clinical and laboratory data of the study population are depicted in (Table I). Compared with the low hs-CRP-level group (n=84), in the elevated hs-CRP-level group (n=27), the age was higher, and there also was a higher proportion of diabetes, a higher proportion of bleeding on probing, and higher gingival index, PPD, and CAL scores. In addition, patients with elevated hs-CRP had less HD time. Other clinical characteristics between groups were not statistically significant.

High-sensitivity CRP levels exhibited a significant positive correlation with age, gingival index, PPD and loss of CAL. Additionally, there was a significant inverse correlation between hs-CRP level and HD time. There were no other significant correlations between hs-CRP levels and other variables (Table II).

Clinical data that possibly contribute to systemic inflammation in patients with chronic HD were entered as covariates in a multiple linear regression model. The final model is presented in Table III. Independent contributors of hs-CRP, thus systemic

TABLE I
CLINICAL AND LABORATORY DATA OF STUDY POPULATION

	Low hs-CRP (n=84)	High hs-CRP (n=27)	p
Age (years)	40.9 (17.6)	49.4 (17.2)	0.03
Gender (masculine)	40 (47.6)	14 (51.8)	0.70
Diabetes	32 (38.0)	19 (70.3)	0.01
Hypertension	74 (88.0)	23 (85.1)	0.69
Active smokers	6 (7.1)	1 (3.7)	0.52
Smoking index (packs/year)	0.8 (2.5)	0.6 (2.0)	0.62
BMI (kg/m^2)	23.5 (3.7)	23.9 (3.5)	0.56
HD time (months)	31.6 (33.1)	13.0 (13.1)	<0.001
Lost teeth (number)	5.7 (8.1)	8.4 (9.2)	0.18
Dental brush removal (months)	4.4 (3.9)	7.2 (7.6)	0.08
Probing bleeding	42 (50.0)	20 (74.0)	0.04
Gingival index	2.1 (0.3)	2.3 (0.3)	0.01
Plaque index	2.2 (0.5)	2.4 (0.6)	0.12
PPD (mm)	2.8 (0.6)	3.6 (0.9)	<0.001
CAL (mm)	3.9 (1.7)	5.1 (2.1)	0.01
hs-CRP (mg/dL)	0.4 (0.3)	3.2 (2.8)	<0.001

Categorical variables are reported as frequency (%) and continuous variables as mean (Standard Deviation [SD]). hs-CRP, high-sensitivity C-reactive protein; BMI, Body mass index; HD, Hemodialysis; PPD, Periodontal pocket depth; CAL, loss of Clinical attachment level. Conversion factors for units: hs-CRP in mg/dL into nmol/dL × 9.524.

TABLE II
CORRELATION BETWEEN HS-CRP AND OTHER VARIABLES

	r (95% CI)	p
Age	0.23 (0.04 – 0.41)	0.01
Smoking index	0.09 (-0.09 – 0.28)	0.31
Body mass index	0.14 (-0.04 – 0.32)	0.13
Gingival index	0.24 (0.05 – 0.41)	0.01
Loss of CAL	0.36 (0.18 – 0.51)	<0.001
PPD	0.52 (0.36 – 0.65)	<0.001

95% CI, 95% Confidence Interval; hs-CRP, high-sensitivity C-reactive protein; CAL, Clinical attachment level; PPD, Periodontal pocket depth.

TABLE III
MULTIPLE LINEAR REGRESSION SHOWING FACTORS INDEPENDENTLY ASSOCIATED WITH HS-CRP

	Regression coefficient β log	Regression coefficient β (95% CI)	Eta $(\eta)^2$	p
Diabetes	0.355	2.2 (1.01 – 5.1)	4%	<0.05
PPD	0.680	4.7 (2.8 – 8.1)	25%	<0.001

95% CI, 95% Confidence Interval; hs-CRP, high-sensitivity C-reactive protein; PPD, Periodontal pocket depth. Covariates entered in initial model: age; gender; diabetes; hemodialysis time; hypertension; smoking index; Body mass index (BMI); active smoking; gingival index; Periodontal pocket depth (PPD), and loss of Clinical attachment level (CAL). Adjusted R^2: 0.303; p<0.001.

inflammation, comprised diabetes and PPD. The model had an adjusted R^2 of 0.30. Other covariables were not statistically significant.

DISCUSSION

In the present study, it was found that patients with elevated hs-CRP levels were older, had a higher frequency of diabetes, and worse periodontal health. Moreover, hs-CRP levels possessed a significant correlation with relevant periodontal parameters as gingival index, loss of CAL, and PPD. In the multiple regression model, diabetes mellitus and PPD were independent contributors of systemic inflammation measurements such as CRP.

Cardiovascular complications are the leading cause of death in population with CKD. There has been more evidence of systemic inflammation as a non-conventional risk factor for accelerated atherosclerosis in this population (3-5). Previous studies have demonstrated abnormal inflammatory biomarkers levels in 30–60% of all patients on HD (22). Such markers, including CRP, are associated with increased risk of cardiovascular disease (CVD) and death (4,5).

Periodontitis has been identified as a risk factor for CVD through chronic systemic inflammation (23,24). Chronic subgingival infection with predominantly Gram-negative anaerobic bacteria can stimulate an acute-phase response and induce to continuous production of circulating cytokines, which may increase inflammatory activity in atherosclerotic lesions, potentially increasing the risk of cardiac and cerebrovascular events. According to previous studies, the association between PD and CKD was not significantly different when the population is divided in subgroups (race, poverty status, educational attainment); however, in those with lower dental care, the association over time may be more profound (25).

Previous reports have demonstrated an association between periodontal disease and elevated CRP levels in patients with chronic HD (12), patients with continuous, ambulatory peritoneal dialysis, and patients on HD (26-29). Moreover, intervention studies have shown that treating periodontal disease reduces serum inflammatory markers such as CRP both in patients on HD and in those on peritoneal dialysis (30,31).

Previous studies have demonstrated that hemodialysis patients showed greater clinical attachment loss and higher values of plaque index when they were compared with early stages of renal disease, which suggests that patients with renal involvement should have a multidisciplinary approach to an improvement of oral and medical conditions (32).

In the present study, full-mouth periodontal examination –considered the "gold standard" of periodontal evaluation– with validation of reproducibility of periodontal measurements and statistical analysis without missing data, comprise some significant strengths. Moreover, based on existing evidence, a linear regression model was designed, incorporating meaningful confounding factors for elevated CRP levels. However, this study has some limitations: the cross-sectional study design prevented assesses temporality. This factor did not allow for a follow-up of patients over time and to evaluate the possible changes in CRP levels depending on the degree of severity of the periodontal disease, or the influence of control of plaque or periodontal therapy; which would have also helped to elucidate the possible effect of the treatment in reducing the CRP levels in these patients. The patients analyzed do not have health insurance coverage, thus limited in terms of raising the assessment to other stratum. The exclusion of patients with infection was based on clinical criteria, which does not ensure the proper classification of asymptomatic carriers and finally, another possible limitation of the study was that serum creatinine was not considered in the analysis as another independent factor, since these values are modified after hemodialysis sessions and CRP values remained relatively stable (33).

A multinational cohort study demonstrated that patients treated with long-term hemodialysis and under preventive dental health practices were associated with better survival than those with poor dental health status (34). Also, it have been evaluated the association between prevalent CKD and chronic oral and systemic inflammatory burden measured by clinical inflammatory periodontal status, systemic antibody response to periodontal pathogens and C-reactive protein, highlight that the next potential step is to consider periodontal therapy as a means to contribute to reducing the chronic inflammatory burden (35). In this sense, although it was not the main objective of the present study, an interesting data found was the inverse correlation between hs-CRP and HD time. This result can be explained as follow: On admission to HD program, patients undergo to plaque control and initial dental education program and at each HD sessions; thus it can be suggested that the longer period of HD also coincides with a greater number of sessions of education; which has been shown in other studies that assess the levels of CRP before and after periodontal therapy in this type of patients and concluded that non-surgical periodontal treatment can effectively reduce the serum level of CRP in these patients (30,36).

As has been mentioned, recent reports showed a concomitant impact of high sensitivity CRP and renal dysfunction. Also, it has been found that concurrent elevation of serum creatinine and CRP are a predictive factor for acute myocardial infarction and chronic kidney disease (37,38). As in these conditions or in ESRD in chronic HD, the mechanisms underlying the simultaneous elevation of serum creatinine and CRP should be evaluated and further investigations are necessary.

This study found evidence consistent with our hypothesis that, in patients on chronic HD, PPD is an independent contributor of systemic inflammation measured as CRP levels in serum. Given the consistency of this association found through several studies and the strong association between systemic inflammation and CKD, health education should be instituted to promote the consideration of periodontal health as part of the management of all patients with CKD on hemodialysis.

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