Relation between ultra-sensitive C-reactive protein, diabetes and periodontal disease in patients with and without myocardial infarction

Relação entre a proteína C ultrarreativa, diabetes e doença periodontal em pacientes com ou sem infarto do miocárdio

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ABSTRACT

Objective: The purpose of this study was to evaluate the impact of diabetes and periodontal disease in us-CRP, an inflammatory marker in patients with and without acute myocardial infarction (AMI). **Subjects and methods:** A case-control study was conducted in 401 subjects aged between 30 and 75 years, living in Bogotá D.C. (Colombia). Patients arriving at the emergency room of the San Ignacio University Hospital with AMI were included into the case group. The control group was defined as those subjects without AMI. The following blood tests were performed: complete blood count (CBC), glycemia, total cholesterol, triglycerides, cHDL, cLDL, and us-CRP. Patients with infections or antibiotic treatment within the last three months, who had received periodontal treatment within the six months prior to the study entry, had oral ulcerations, or less than seven teeth were excluded from the study. Periodontal disease was diagnosed based on the 1999 Armitage's classification. **Results:** The mean us-CRP value found in diabetic patients with severe chronic periodontitis was 5.31 mg/L (SD 6.82), and 2.38 mg/L (SD 4.42) in non-diabetic patients, being statistically significant (p = 0.000). **Conclusion:** Diabetes had an impact in periodontal disease and us-CRP. In patients with AMI, DM and PD considerably increased the us-CRP. Arq Bras Endocrinol Metab. 2014;58(4):362-8

Keywords
Diabetes mellitus; periodontal disease; cardiovascular disease; inflammation; C-reactive protein

RESUMO

Objetivo: O objetivo deste estudo foi avaliar o impacto do diabetes e da doença periodontal na us-CRP, um marcador inflamatório em pacientes com ou sem infarto agudo do miocárdio (IAM). **Sujeitos e métodos:** Um estudo caso-controle foi conduzido em 401 sujeitos com idades entre 30 e 75 anos que moravam em Bogotá D.C. (Colômbia). Os pacientes que chegavam ao pronto-socorro do hospital universitário de San Ignacio com IAM foram incluídos no grupo caso. O grupo controle foi definido por sujeitos sem IAM. Foram feitos os seguintes exames de sangue: contagem total de eritrócitos (CTE), glicemia, colesterol total, triglicérides, cHDL, cLDL e us-CRP. Os pacientes com infecções ou em tratamento com antibióticos nos últimos três meses, que receberam tratamentos periodontal nos seis meses anteriores ao estudo, tinham úlceras orais ou menos de sete dentes foram excluídos do estudo. A classificação de Armitage de 1999 foi usada para definir a doença periodontal. **Resultados:** O valor médio de us-CRP observados em pacientes diabéticos com periodontite crônica grave foi 5,31 mg/L (SD 6,82) e 2,38 mg/L (SD 4,42) em pacientes não diabéticos, um valor estatisticamente significativo (p = 0,000). **Conclusão:** O diabetes tem um impacto na doença periodontal e na us-CRP. Em pacientes com IAM, DM e DP, a us-CRP foi consideravelmente mais alta. Arq Bras Endocrinol Metab. 2014;58(4):362-8

Descritores
Diabetes melito; doença periodontal; doença cardiovascular; inflamação; proteína C reativa

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INTRODUCTION

Cardiovascular disease is a multifactorial disease, of high prevalence in developed countries, and its prevalence is rapidly increasing in developing countries. Acute myocardial infarction (AMI), its more dramatic outcome, is the first cause of death worldwide.

It has been reported that diseases that produce a systemic inflammatory response, such as *diabetes mellitus* (DM) and periodontal disease (PD) can influence the etiopathogenesis of cardiovascular disease, elevate the pro-inflammatory cytokine levels and increase CRP. DM and periodontitis are both chronic inflammatory diseases in which lack of control and severity of one of them can negatively influence the other. Recent studies have demonstrated that patients with DM have an increased risk of developing periodontitis, and that diabetes is more difficult to be controlled in those patients (1).

The relationship between PD and its condition as a risk factor for systemic diseases has been investigated during the past two decades. Current knowledge about the pathology of periodontal disease as a high prevalent chronic infection in the population worldwide enables the establishment of three basic aspects to understand the eventual association: the risk factors shared between PD and related systemic diseases, the presence of a subgingival biofilm that is the source of gram-negative bacteria, and the existence of the typical lesion in PD, the periodontal pocket, as a reservoir of inflammatory mediators.

DM is a chronic disease that is also considered a high-impact disease in public health worldwide. This condition requires a lifelong management to reduce its high morbidity and, in the same extent, to reduce premature death caused by its associated complications (2). Hyperglycemia in DM induces a non-enzymatic glycosylation of proteins, which results in an increase of advanced glycation end-products (AGES). AGES stimulate macrophages to activate the expression of cytokines, such as IL-6 and TNF-α. These cytokines then induce the liver to secrete acute-phase reactants, such as CRP and fibrinogen. It has also been described that the expression of those inflammatory mediators involved in hyperglycemia are also associated with periodontal disease and with an increased risk of cardiovascular disease (3).

The literature has focused on analyzing the influence of DM in the development of periodontal disease. In 2012, Abdo and cols., analyzed the effect of these systemic conditions on periodontal disease in 56 patients with DM, 67 with dyslipidemia, and 74 with dyslipidemia and DM. Their study concluded that dyslipidemia had no influence on periodontal disease, but DM was significantly associated with the loss of periodontal attachment levels (4).

It is evident that PD and DM are mutually related and that, in both, PD and DM, an increase in pro-inflammatory cytokines and CRP is evidenced. Us-CRP levels greater than 2.0 mg/mL have been related with higher risk of cardiovascular and cerebrovascular events.

Besides, the high plasmatic levels of IL-6 have been associated to unstable angina and cardiovascular disease, and it has been established that IL-6 induces CRP. Steel and cols. (5) and Loos and cols. (6) showed that periodontitis increases the systemic levels of us-CRP, IL-6, and neutrophils, which produce an increase of the inflammatory activity in atherosclerotic lesions, and potentially increases the risk of cardiovascular and cerebrovascular events (7).

Based on these considerations, the purpose of this study was to evaluate the impact of diabetes and periodontal disease in the us-CRP marker in patients with and without acute myocardial infarction.

MATERIALS AND METHODS

A case-control study in 401 subjects aged between 30 and 75 years was conducted in Bogota, Colombia. Enrolled patients attended the dental clinics of the School of Dentistry at the Pontificia Universidad Javeriana, emergency room of San Ignacio University Hospital, and the hospital services of Fundación CardioInfantil.

The TAMAMU 1.1® program was used to estimate the sample size considering a type I error of 0.05; standard deviation of 3.5; and population mean of 1.0. The sample size for this study was 401 patients, 200 patients in the case group, and 201 patients in the control group.

This study was approved by the corresponding EC/IRBs and complied with all regulatory guidelines to be classified as a minimum risk research. Each subject signed a consent form in order to take part in the study.

The case group included those patients arriving at the emergency room of the San Ignacio University Hospital with acute myocardial infarction (AMI), diagnosed by sudden retrosternal chest pain with a minimum duration of 30 minutes and ischemic changes in the electrocardiogram confirmed by specific markers (CK or troponin). The following blood tests were per-

formed: total CK, MB CK, troponin I, CBC, creatinine, electrolytes, glycemia, total cholesterol, triglycerides, cHDL and cLDL; electrocardiograms were also performed.

Once the patient was stabilized, the consent form was signed 24 to 48 hours after the stabilization. A blood sample was taken to obtain the us-CRP values. The control group included patients without AMI. Blood samples were taken for lab tests (CBC, glycemia, total cholesterol, triglycerides, cHDL, cLDL, and us-PCR). Patients with infections or antibiotic treatment within the previous three months, or who had undergone periodontal treatment within 6 months prior to the study, or patients with oral ulcerations caused by any prosthesis, candidiasis or stomatitis, and those who had less than seven teeth were excluded from the study.

The periodontal examination of the two groups was performed by three examiners, previously calibrated with the Florida electronic probe. Periodontal disease was diagnosed based on the 1999 classification system developed by Armitage. The us-CRP assessment was performed by the IMMULITEC method, which contains a monoclonal antibody and anti-CRP polyclonal antibody. The method provides measurement ranging from 0.1 to 500 mg/L.

Statistical analysis

The statistical analysis of the variables was performed using means and standard deviations. In order to determine the differences between groups, Pearson's chi square test was used and, in all cases, a p value < 0.05 was defined as the limit for statistical significance. Indirect relative risk measures (Odds ratios) were used in the final analysis.

RESULTS

A total of 56.1% (225) of the 401 patients were male, with mean age of 52.5 years and older than women by 5 years (p < 0.05). The study groups were different in the following characteristics: AMI patients had a mean age of 58 years while the non-infarction group showed mean age of 47 years, with a statistically significant difference (p < 0.05), although without clinical significance for CD or PD.

A total of 50 patients (25%) from the case group, and 7 (3.48%) from the control group, had diabetes, with an OR of 9.24 (CI 95% 4.07 – 2.49). Among the AMI cases, 161 patients (82.14%) had periodontal disease (moderate chronic periodontitis or advanced chronic periodontitis), while 79 subjects (39.7%) in the control group had PD with an OR of 6.99 (CI 95% 4.40 – 11.1).

Regarding us-CRP values, a mean of 4.1 mg/L was found in the case group, considered high for this group (p < 0.05). When comparing glucose values, the case group showed higher levels in 27.8 mg/dL compared with the control group (p < 0.05). A similar finding was observed in the case group with triglycerides, which was 30.3 mg/dL higher (p < 0.05). HDL was 12.6 mg/L lower in AMI patients (p < 0.05). In addition, greater dyslipidemia, high blood pressure, and more teeth were found in this group (p < 0.05) (Table 1).

Table 1. Descriptive analysis of the population

	Controls n = 201	Cases n = 200	P Value
Men	61 (30.4%)	164 (82%)	< 0.0001
Age (mean, SD)	47 (13.1)	58 (11.5)	< 0.0001
Glycemia (mean, SD)	96.8 (26.2)	124.6 (48.5)	< 0.0001
Triglycerides > 150 mg/dL	79 (39.3%)	108 (54%)	0.003
Total cholesterol (mean, SD)	214.2 (45.8)	195.8 (49.5)	0.0001
cHDL < 40 mg/L	141 (70.2%)	51 (25.5%)	< 0.001
LDL > 100	164 (81.6%)	157 (78.5%)	0.439
Diabetes	7 (3.5%)	50 (25%)	< 0.0001
Dyslipidemia	39 (19.4%)	88 (44%)	< 0.0001
High blood pressure	21 (10.5%)	105 (52.5%)	< 0.0001
Smoking	23 (11.5%)	48 (24.9%)	< 0.0001
# Teeth			
7 – 10	4 (2%)	21 (10.5%)	
11 – 20	44 (21.9%)	70 (35%)	< 0.0001
21 – 32	153 (76.1%)	109 (54.5%)	
Carbohydrate intolerance	8 (3.9%)	68 (34%)	< 0.0001
CRP > 2 mg/L	1 (0.5%)	105 (52.5%)	< 0.0001
Attachment loss	130 (64.7%)	179 (89.5)	< 0.0001

DM patients were 6.3 years older than non-diabetics; us-CRP values were 3.3 mg/L higher, as well as cholesterol, in 19.3 mg/dL and glycemia, in 74.8 mg/dL, a statistically significant difference (p < 0.05). On the contrary, HDL was 9.07 mg/dL lower (p < 0.05) in diabetic patients, and so were dyslipidemia, high blood pressure, smoking, and in males (p < 0.05).

The analysis of the behavior of periodontal disease according to diabetes showed that 43 (75.4%) of the

57 diabetic patients had ACP, followed by 12.2% with MCP, different from what was observed in the non-diabetic group, in which 194 subjects (56.3%) had ACP, followed by gingivitis with pre-existing attachment loss in 53 subjects (15.4%), although not statistically significant (p = 0.052) (Table 2).

Table 2. Distribution of periodontal disease in relation to diabetes

Periodontal diagnosis	Diabetes		Total
	Yes	Not	
Reduced healthy periodontium (RHP)	0	15	15
Simple gingivitis (SG)	0	18	18
Gingivitis with pre-existing attachment loss (GPAL)	6	53	59
Incipient chronic periodontitis (ICP)	1	21	22
Moderated chronic periodontitis (MCP)	7	43	50
Advanced chronic periodontitis (ACP)	43	194	237

The analysis of us-CRP values in the diabetic group, it was found that the mean value was 5.15 mg/L (SD 6.6), different from what was observed in the non-diabetes group, 1.82 mg/L (SD 3.82) ($p \leq 0.05$). As to the carbohydrate intolerants, it was observed that the mean was 4.04 mg/L (SD 5.26) compared with non-intolerants,1.89 mg/L (SD 4.18) ($p \leq 0.05$).

As for us-CRP behavior according to periodontal diagnosis, it was observed that the mean was 2.92 mg/L (SD 5.06) in ACP, followed by 1.77 mg/L (SD 3.45) in MCP, and 1.74 mg/L (SD 3.32) in ICP (Table 3).

Table 3. Us-CRP according to periodontal diagnosis

Periodontal diagnosis	us-CRP	
	Mean	Standard deviation
Reduced healthy periodontium (RHP)	0.358	0.737
Simple gingivitis (SG)	0.237	0.232
Gingivitis with pre-existing attachment loss (GPAL)	1.549	3.855
Incipient chronic periodontitis (ICP)	1.741	3.321
Moderated chronic periodontitis (MCP)	1.778	3.457
Advanced chronic periodontitis (ACP)	2.92	5.06

Analyzing the us-CRP values according to periodontal disease and the presence of diabetes or not, it was observed that the mean for diabetic patients with ACP was 5.31 mg/L (SD 6.82), and the mean in non-diabetic patients with ACP was 2.38 mg/L (SD 4.42), with a statistically significant difference (p = 0.000) (Table 4).

Table 4. Us-CRP according to diabetes and periodontal disease

Diabetes	Periodontal diagnosis	us-CRP	
		Mean	Standard deviation
Yes	Reduced healthy periodontium (RHP)	0	0
	Simple gingivitis (SG)	0	0
	Gingivitis with pre-existing attachment loss (GPAL)	6.97	8.73
	Incipient chronic periodontitis (ICP)	1.24	.
	Moderated chronic periodontitis (MCP)	3.19	2.47
	Advanced chronic periodontitis (ACP)	5.31	6.82
Not	Reduced healthy periodontium (RHP)	0	0
	Simple gingivitis (SG)	0.23	0.23
	Gingivitis with pre-existing attachment loss (GPAL)	0.93	2.33
	Incipient chronic periodontitis (ICP)	1.76	3.4
	Moderated chronic periodontitis (MCP)	1.54	3.56
	Advanced chronic periodontitis (ACP)	2.38	4.42

When evaluating the impact of diabetes in periodontal disease and the inflammatory marker us-CRP according to the group (AMI and non-AMI), it was found that, in the group of patients with AMI, ACP and diabetes, the us-CRP value was 6.16 (SD 0.649) compared with the non-diabetes group, in which the value was 4.19 (SD 0.385). Regarding the non-AMI group, the us-CRP value for patients with ACP and diabetes was 0.103 (SD 1.612) compared with the non-diabetes group, whose value was 0.258 (SD 0.419), without a statistically significant difference between the groups (p = 0.585) (Table 5).

It was observed that there was a trend of higher us-CRP values in diabetic patients with ACP. In patients with AMI, diabetes and periodontal disease, us-CRP wsa considerably increased.

DISCUSSION

The results from this study showed that in patients with AMI, it was 9.24 times more frequent to find diabetes and 6.99 times more common to find periodontal disease than in patients without AMI.

Patients with AMI showed increased CRP as well as multiple risk factors, such as dyslipidemia, diabetes. and high blood pressure. In the comparison of patients with AMI with patients without AMI, higher levels of CRP (4.1 mg/L) were found, as well increased glucose by 27.8 mg/dL and triglycerides by 30.3 mg/dL, and

Table 5. Us-CRP according to AMI, diabetes and periodontal disease

Group	Periodontal diagnosis	Diabetes	us-CRP	
			Mean	Standard deviation
Case	Reduced healthy periodontium (RHP)	No	1.86	2.79
		Yes	.	.
	Simple gingivitis (SG)	No	0.56	3.94
		Yes	.	.
	Gingivitis with pre-existing attachment loss (GPAL)	No	3.27	1.09
		Yes	8.30	1.76
	Incipient chronic periodontitis (ICP)	No	2.73	1.09
		Yes	1.24	3.94
	Moderated chronic periodontitis (MCP)	No	3.75	0.98
		Yes	3.19	1.49
	Advanced chronic periodontitis (ACP)	No	4.19	0.38
		Yes	6.16	0.64
Control	Reduced healthy periodontium (RHP)	No	0.12	1.09
		Yes	.	.
	Simple gingivitis (SG)	No	0.21	0.95
		Yes	.	.
	Gingivitis with pre-existing attachment loss (GPAL)	No	0.17	0.62
		Yes	0.31	3.94
	Incipient chronic periodontitis (ICP)	No	0.18	1.39
		Yes	.	.
	Moderated chronic periodontitis (MCP)	No	0.23	0.76
		Yes	.	.
	Advanced chronic periodontitis (ACP)	No	0.25	0.41
		Yes	0.10	1.61

dyslipidemia in AMI patients, while HDL was lower in those patients (12.6 mg/dL). Furthermore, higher blood pressure was found in this group ($p < 0.05$). These findings confirm that the cardiovascular disease is a multifactorial condition, being in agreement with the results obtained by Skoumas and cols. (8) in whose report the analysis of cardio-metabolic risk factors showed DM and high blood pressure in patients with hyperlipidemia as major risk factors.

When periodontal disease was analyzed according to diabetes, it was found that 48 of 55 diabetic subjects had periodontal disease (87.2%), while 233 of 340 of non-diabetics had the disease (68.5%), with an odds ratio of 3.15 (IC95% 1.38-7.19). Sub-group analysis showed that 43 of 55 (78.1%) diabetic subjects had ACP, followed by MCP in 12.2% of the subjects; these results are in agreement with the report by Salvi and cols. who stated that diabetes could be considered a risk factor for periodontal disease (9), and by Mealey and Ocampo who declared that the risk of periodontitis approximately increased three-fold in diabetics compared with non-diabetic patients (10). The literature has supported the fact that DM can predispose patients to periodontitis, and contribute to its pathogenesis due to vascular compromise, deficit of cell-mediated immunity and high level of blood glucose, which could increase bacterial growth (11).

The biological plausibility could be related to a hyperglycemic condition in diabetes, which induces non-enzymatic glycosylation of proteins, deriving an increase of advanced glycation end-products (AGES). The AGES stimulate macrophages to produce cytokines, such as Interleukin 6 (IL-6) and TNF-alpha. These cytokines induce the liver to secrete acute phase reactants, such as CRP and fibrinogen. The expression of the same inflammatory mediators involved in hyperglycemia has been reported as associated with periodontal disease, as well as risk factors for cardiovascular disease (12).

When us-CRP was analyzed, a higher mean value, 5.15 mg/L (SD 6.6), was found in the diabetes group, different from what was observed in the non-diabetes group, in which the mean value was 1.82 mg/L (SD.3.82) ($p \leq 0.05$).

US-CRP is increased in endothelial dysfunction and in atherogenesis, and its increased levels have been associated with macrovascular disease and non-ocular microvascular conditions in type 2 diabetes. Also, it has

been related with high adiposity, mainly abdominal, insulin resistance, and dyslipidemia. CRP directly triggers the NO_2 production, which ends in endothelial dysfunction (13). The Atherosclerosis Risk in Communities Study (14) found an association between systemic inflammation, development of type 2 diabetes and cardiovascular diseases.

This study also showed an increase in us-CRP in patients with ACP, with a mean of 2.92 mg/L (SD 5.06) followed by MCP with 1.77 mg/L (SD 3.45), and incipient chronic periodontitis 1.74 mg/L (SD 3.32). These results confirm those previously presented by Steel and cols. (15) and Loos and cols. (16), who stated that periodontitis increased systemic levels of C-reactive protein, IL-6 and neutrophils, which could increase the inflammatory activity in atherosclerotic lesions and potentially increase the risk of cardiac and cerebrovascular events (17).

Kanaparthy and cols. in 2012 (18) also evaluated the us-CRP levels in subjects with aggressive periodontitis and chronic periodontitis, and compared these levels with those of healthy patients. They reported that patients with aggressive periodontitis (CRP 4.5 mg/L) and chronic periodontitis (CRP 6.06 mg/L) showed higher CRP levels than healthy patients (1.01 mg/L), but indicated that their results could not be conclusive regarding the direct relation between periodontal disease and us-CRP, due to the sample size of 45 patients, 15 per group.

The inflammatory mediators, such as CRP, are increased in the bloodstream of subjects with periodontal disease, suggesting that the systemic inflammation triggered by the periodontal infection directly contributes to the elevation of acute phase reactant in plasma, or produced by distant organs, such as the liver. These proteins can also cause harmful effects in target organs by modeling pathologic processes, such as atherosclerosis. Higher CRP levels, IL-6 and neutrophils in patients with periodontitis may occur when bacteria, their products, and cytokines enter the bloodstream (19,20).

Kodovazenitis and cols. (21) conducted a study to analyze the relationship between periodontal disease and CRP in AMI patients. A total of 47 AMI patients and 40 patients with non-obstructive coronary disease were enrolled; smoking and diabetic patients were excluded. Their results showed that periodontal disease was more frequent in AMI patients than in patients with non-obstructive coronary disease. The presence of the disease was related to higher levels of CRP in both groups, and they concluded that periodontal disease contributed to increase the inflammatory marker CRP in non-diabetic and non-smokers, which suggests the relevance of periodontal disease control in the reduction of the risk of AMI.

When analyzing us-CRP values in patients with periodontal disease and with or without diabetes, it was observed that the mean CRP value in diabetic patients with ACP was 5.31 mg/L (SD 6.82), and 2.38 mg/L (SD 4.42) in non-diabetics with ACP, with a statistically significant difference.

Diabetes is a high-impact disease and its relation with periodontal disease has been previously investigated. Khader and cols. (22) conducted a meta-analysis that included 18 cross-sectional studies, 3 prospective studies, and 2 RCT, in which oral hygiene and periodontal condition were analyzed. They reported that people with diabetes experienced more severe periodontal disease, with statistically significant differences ($p = 0.000$) (23).

By evaluating the relation between diabetes and periodontal disease and us-CRP in patients with and without AMI, it was found that in the group of patients with AMI, diabetes and ACP, us-CRP value was 6.16 (SD 0.649) compared with the non-diabetes group, in which the CRP value was 4.19 (SD. 0.385). In relation to the non-AMI group, the us-CRP value in patients with ACP and diabetes was 0.103 (SD 1.612) compared with the non-diabetic group 0.258 (SD 0.419), ($p = 0.585$).

It was evidenced that the presence of diabetes or periodontitis significantly increased CRP. The presence of the three conditions: diabetes, periodontitis, and AMI increased CRP up to 6.16 mg/L.

Glurich and cols. (24) analyzed and compared the CRP concentration in healthy subjects as well as in patients with periodontal and cardiovascular disease; and reported that CRP doubled its concentration in patients with one of these conditions and increased 5-fold when the two were present. It has been found that CRP as a systemic inflammatory marker is an independent risk factor for patients with recurrent ischemia and unstable angina.

Regardless of the triggering mechanism, systemic inflammation seems to be the focal point which would explain the elevation in CRP observed in patients with DM and PD. The moderate elevation of CRP within the normal range in healthy subjects has been a predictor for subsequent coronary events after some years,

in patients with angina or normal subjects. This data shows the presence of a possible low-grade inflammation in coronary arteries, specifically in the subendothelial space, or can suggest an inflammatory process or prothrombotic effects that increase CRP (25,26).

In light of the results of this study, we can conclude that patients with AMI have more conventional risk factors, such as diabetes, dyslipidemia, and high blood pressure, and have an increased probability of having periodontal disease, which is more severe than in patients with no infarction.

Also, a more severe periodontal disease was found in diabetics than in non-diabetics.

Us-CRP was higher in diabetics and in glucose-intolerant patients than in non-diabetics and non- glucose-intolerant ones.

A trend to higher us-CRP values was observed in diabetic patients with advanced chronic periodontitis than in those with other periodontal conditions.

Diabetes had an impact in periodontal disease and in us-CRP inflammatory marker. In patients with AMI, DM and PD, us-CRP was considerably increased.

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