

Relationship between periodontal status and C-reactive protein and interleukin-6 levels among atherosclerotic patients in Bandar Abbas, Iran in 2014Ruhollah Etemadifar¹, Shokufe Konarizadeh², Atefeh Zarei², Hossein Farshidi³, Alireza Sobhani⁴¹ Periodontologist, Assistant Professor, Hormozgan University of Medical Sciences, Bandar Abbas, Iran² Dentistry Student, Hormozgan University of Medical Sciences, Bandar Abbas, Iran³ Cardiologist, Associate Professor, Hormozgan University of Medical Sciences, Bandar Abbas, Iran⁴ Pathologist, Assistant Professor, Hormozgan University of Medical Sciences, Bandar Abbas, Iran**Type of article:** Original**Abstract**

Background: Recent studies have reported an association between periodontitis and cardiovascular diseases. Atherosclerosis is also a risk factor for cardiovascular diseases. IL-6 and CRP are important inflammatory markers that are important because they have been shown to be higher when a patient has periodontitis, and they are related to atherosclerosis. The aim of this study was to assess the relationship between periodontitis and CRP and IL-6 in atherosclerotic patients.

Methods: The study population in this case control study was atherosclerotic patients in Bandar Abbas, Iran in 2014. The participants included 30 individuals with periodontal diseases and 30 individuals without periodontal diseases, and they were allocated into two groups according to probe depth (PD) and clinical attachment loss (CAL). Inflammatory markers, including CRP and IL-6 were measured in the two groups. The data were analyzed using IBM SPSS 21 statistical software. Descriptive statistics, chi-squared, independent samples t-test, and Mann-Whitney tests were used to analyze the data.

Results: Individuals with abnormal CRP had significantly higher PD and CAL than individuals with normal CRP ($P < 0.001$). Although PD was not significantly different in individuals with normal and abnormal IL-6 ($P = 0.124$), CAL was significantly higher in individuals with abnormal IL-6 than in the other individuals ($P = 0.005$).

Conclusion: The results of this study showed that CRP and IL-6 are associated with periodontal diseases in atherosclerotic patients. Treatment of periodontal diseases is recommended in atherosclerotic patients.

Keywords: periodontal diseases, atherosclerosis, probe depth (PD), clinical attachment loss (CAL)

1. Introduction

Local dental and oral infections can lead to systemic inflammation via different mechanisms. These mechanisms can explain the association between periodontitis and cardiovascular diseases (1). Several studies have shown the association between periodontitis and cardiovascular disease, atherosclerosis, systemic inflammation, and myocardial infarction. However, the mechanisms are not completely understood. Periodontitis is chronic dental and oral inflammation that is characterized by plaque formation and increase in probe depth (PD) and clinical attachment loss (CAL). Atherosclerotic vascular diseases are the most common causes of death, accounting for about 30% of mortality and morbidity in the world (2). Systemic inflammation plays an important role in the atherosclerotic process, and systemic inflammation biomarkers, including CRP and IL-6, increase in atherosclerotic patients (3, 4).

Corresponding author:

Dr. Alireza Sobhani, Hormozgan University of Medical Sciences (HUMS), Hormozgan, Iran. Tel: +98.9173611180, Email: arsobhani1344@yahoo.com

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The mechanisms of the relationship between periodontitis and cardiovascular diseases are not completely understood, but some direct and indirect pathways have been shown to be responsible for this relationship. Increase in the levels of CRP, IL-1, IL-6, and IL-8 is the mechanism that can indirectly increase the risk of atherosclerosis and cardiovascular diseases in patients with periodontitis (5-19). Also, some of the pathogens that play a role in periodontitis can increase the risk of atherosclerosis and cardiovascular diseases (20-30). Although periodontitis and cardiovascular diseases have common risk factors, including diabetes mellitus, smoking, and increase in age, several studies have shown that the relationship between periodontitis and cardiovascular diseases is independent of other classical risk factors of cardiovascular diseases (31). Atherosclerosis is the most important risk factor of cardiovascular diseases. Its association with periodontitis has been shown in several studies, but the mechanisms are not completely clear. Systemic inflammation may play a role in this association. The general objective of this study was to determine the association between periodontitis and CRP and IL-6 in atherosclerotic patients. The specific objectives were:

- 1) To determine the association between periodontitis and CRP in atherosclerotic patients
- 2) To determine the association between periodontitis and IL-6 in atherosclerotic patients

2. Materials and Methods

2.1. Study setting

This case-control study was conducted with atherosclerotic patients who had undergone angiography in Shahid Mohammadi Hospital in 2014. The study population was patients who had undergone selective percutaneous coronary intervention (PCI) in Shahid Mohammadi Hospital. Patients were examined for periodontitis and were divided into two groups, i.e., a case group that included people with periodontitis and a control group of people who did not have periodontitis. The first 30 patients who met the inclusion criteria were enrolled in the two groups. The sample size was decided based on the formula that considers the power of 80% and a significance level of 0.05 ($Z_{\beta}=0.84$; $Z_{\alpha}=1.96$). In this formula, r is assumed to be 1 when the numbers of cases and control are the same. Considering positive inflammatory markers of about 40% in the case group and 10% in control group, a sample size of at least 29 was assumed in each group.

$$n = \left(\frac{r+1}{r} \right) \frac{(\bar{p})(1-\bar{p})(Z_{\beta} + Z_{\alpha/2})^2}{(p_1 - p_2)^2}$$

2.2. Selection criteria

2.2.1. Inclusion criteria

The following were set as the inclusion criteria of the study:

- 1) Elective patients with severe vascular stenosis with percutaneous coronary intervention (PCI)
- 2) Patients who have signed informed consent forms for participation in the study
- 3) Patients who have a dentition of at least 10

2.2.2. Exclusion criteria

The following were set as the exclusion criteria of the study:

- 1) Smokers
- 2) Diabetics
- 3) Antibiotic use in past three months
- 4) Use of NSAIDs
- 5) Use of Corticosteroids
- 6) Use of anti-histamine and a recent myocardial infarction
- 7) Gastrointestinal infections, pneumonia, and other acute infections

2.3. Data collection and measurement tool

2.3.1. Dental physical examination

Each patient was given a dental physical examination by an educated examiner (dentistry student) under the supervision of a dentist. The examination included probe depth (PD), clinical attachment loss (CAL), and bleeding on probing (BOP). The patients were divided into two groups based on the results of their physical examinations, i.e., those with and those without periodontitis. As defined for the control group, no patients had $PD > 3$ mm or $CAL > 1$ mm. Also, individuals in case group had at least six teeth with $PD \geq 5$ mm or $CAL \geq 3$ mm.

2.3.2. Blood samples and laboratory tests

A blood sample was obtained from all the patients and was analyzed in the laboratory to determine the levels of IL-6 and CRP. Both tests were measured quantitatively using the electrochemiluminescence method using an Integra 400 Plus

device and a Cobas E411 made in Germany and roch kits. The results were reported in pg/ml, and the normal range was 0-4.99 pg/ml for CRP and less than 7pg/ml for IL-6.

2.4. Data analysis

The data were analyzed using IBM SPSS 21 statistical software. Descriptive statistical tests were used to analyze the data, including mean and standard deviation for quantitative variables and frequency and percentage for qualitative variables. Also chi-squared, independent samples t-test, and Mann-Whitney tests were used to analyze the data.

2.5. Ethical consideration

The study was approved by the Ethics Committee at Hormozgan University of Medical Sciences. Signed informed consent forms were obtained from all of the patients. The patients were not charged for the costs of the laboratory tests.

3. Results

3.1. Demographic information

We enrolled 60 patients in this study, including 30 cases and 30 controls. Among them, 38 (63.3%) were males and 22 (36.7%) were females. In each group 19 (63.3%) were male and 11 (36.7%) were female, and there were no significant differences between two groups.

3.2. Descriptive analysis of CRP and IL-6

Positive CRP was reported in 12 patients (20%) and 19 patients (31.7%) had positive IL-6. Therefore, CRP and IL-6 were reported to be negative in 48 patients (80%) and 41 patients (68.3%), respectively.

3.3 Descriptive analysis of probing depth (PD) and clinically attachment loss (CAL)

Mean CAL and PD were 2.70 ± 2.16 and 4.13 ± 1.51 , respectively.

3.4 Comparison of laboratory test results between two groups

In the case group, PD and CAL were significantly higher than they were in the control group. Details are shown in Table 1. Table 2 compares the CRP and IL-6 levels in the case and control groups. The results showed that both CRP and IL-6 were significantly greater in the periodontitis group than in the control group. As shown in Table 3, PD and CAL were significantly greater in patients with positive CRP than in patients with negative CRP. Although there was no significant difference in PD according to the IL-6 results, CAL was significantly greater in patients with abnormal IL-6 (Table 4).

Table 1. Comparison of PD* and CAL** in the case and control groups

		Mean±SD	Mean Rank	Sum of Ranks	P value
PD	Case	5.10 ±1.51	42.55	1276.5	<0.001
	Control	3.17±0.64	18.45	553.5	
CAL	Case	4.67±0.88	45.5	1365	<0.001
	Control	0.73±0.86	15.5	465	

* Probe depth; ** Clinical attachment loss

Table 2. Comparison of CRP and IL-6 level in case and control groups

Inflammatory markers		Case group	Control group	P value
CRP	Normal (0-4.99)	18 (60%)	30 (100%)	<0.001
	Abnormal (≥ 5)	12 (40%)	0 (0%)	
IL-6	Normal (up to 7)	14 (46.7%)	27 (90%)	<0.001
	Abnormal (≥ 7)	16 (53.3%)	3 (10%)	

Table 3. Comparison of PD and CAL in patients with normal and abnormal CRP

Index	CRP	n	Mean±SD	Mean Rank	Sum of Ranks	P value
PD	Normal (0-4.99)	48	3.92±1.44	27.71	1330	0.01
	Abnormal (≥5)	12	5±1.53	41.67	500	
CAL	Normal (0-4.99)	48	2.27±2.16	27.38	1314	0.005
	Abnormal (≥5)	12	4.42±1.08	43	516	

* Probe depth; ** Clinical attachment loss

Table 4. Comparison of PD and CAL according to IL-6

Index	IL-6	n	Mean±SD	Mean Rank	Sum of Ranks	P value
PD	Normal (up to 7)	41	4.02±1.55	28.22	1157	0.124
	Abnormal (≥)	19	4.37±1.42	35.42	673	
CAL	Normal (up to 7)	41	2.12±2.02	26.23	1075.5	0.005
	Abnormal (≥)	19	3.95±1.95	39.71	754.5	

* Probe depth; ** Clinical attachment loss

4. Discussion

In recent years, several studies have reported an association between cardiovascular diseases and periodontitis. The atherosclerosis process has been shown to be related to periodontitis in several studies. Atherosclerosis also plays an important role in cardiovascular diseases and is an important risk factor for stroke and myocardial infarction. Inflammation is one important factor that is related to atherosclerosis. Some medications that have been shown to be effective in the prevention and treatment of cardiovascular diseases also have been shown to have anti-inflammatory effects. Statins are a group of lipid-lowering medications that are used extensively for prevention and treatment of cardiovascular diseases. Studies have shown that the anti-inflammatory effect of statins is an important factor in the prevention and treatment of cardiovascular diseases (32). CRP and IL-6 are systemic inflammatory factors that can help detect the activity of inflammatory pathways. Several studies have shown that patients with cardiovascular diseases have higher CRP and IL-6 levels. Also, in patients who have periodontitis, the inflammatory pathways are activated, and this is associated with increased CRP and IL-6 levels. According to results of a study by Kaptoge et al., the association between inflammatory markers, such as CRP, and cardiovascular diseases depends on other cardiovascular risk factors (7). Therefore, it seems that the association between the level of CRP and cardiovascular diseases is greater in patients with risk factors for cardiovascular disease. Several studies have reported the association between periodontitis and cardiovascular diseases. Increase in inflammatory markers may play a role in this association. CRP and IL-6 are significantly higher in patients who have periodontitis (33), and they decrease when the periodontitis is treated (34). Also, some studies have shown that there are relationships between CRP and PD and CRP and CAL in patients with periodontitis (35).

The results of our study indicated that the inflammatory markers were significantly higher in patients with periodontitis. Also higher levels of PD and CAL were reported in patients with positive CRP tests. Although PD was not significantly different in patients with positive and negative IL-6, CAL was significantly higher in patients with positive IL-6. Our results were in good agreement with the results of similar studies. Although the studies were different in methodology, they confirmed the role of inflammatory markers in periodontitis and cardiovascular diseases. Buhlin et al. (2003) showed that CRP, IL-6, and TNF- α were higher in patients with periodontitis who had no history of cardiovascular diseases (36). The higher level of inflammatory markers can facilitate the process of atherosclerosis (14) and increase the rate of the development of cardiovascular diseases. Also, Nakajima et al. in Japan showed higher levels of CRP and IL-6 in periodontitis patients. According to the results of this study, CRP and IL-6 levels decreased with the treatment of periodontal diseases (33). Therefore, it is recommended patients with periodontitis be treated because they are at high risk for cardiovascular diseases (33). Treatment of periodontitis can prevent the process of atherosclerosis (34).

One limitation in our study was that it was not possible for us to match both groups for some factors, e.g., age and lipid profile, that could affect the inflammatory markers. This limitation may have influenced our results. Also, we did not assess other inflammatory markers, and we did not determine the effect of the treatment of periodontitis on the levels of the inflammatory markers.

5. Conclusion

Atherosclerotic patients with periodontitis had higher levels of inflammatory markers than patients in the control group. This finding shows the possible role of inflammatory markers in the relationship between periodontitis and cardiovascular diseases. We recommend that future research focus on the effect of the treatment of periodontitis on the levels of inflammatory markers in atherosclerotic patients.

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Conflict of Interest

There is no conflict of interest to be declared.

Authors' contributions

All authors contributed to this project and article equally. Both authors read and approved the final manuscript.

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