

Association between Periodontal Disease and Elevated C-reactive Protein in Acute Myocardial Infarction Patients

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Abstract:

Statement of problem: Periodontal disease (PD) has been linked to adverse cardiovascular events by unknown mechanisms. C-reactive protein (CRP) is a prognostic marker for cardiovascular disease, with reported elevated serum levels during PD.

Purpose: The aim of the present study was to evaluate the association between PD and higher CRP levels in the serum of acute myocardial infarction (AMI) patients.

Materials and Methods: In this cross-sectional study, periodontal examinations and CRP serum levels were measured in 51 Q-wave and non-Q-wave AMI patients. All assessments were made during index hospitalization and within 72 hours of symptom onset. The patients were divided into two groups based on the presence or absence of PD and were frequency matched for sex, body mass index, smoking and traditional risk factors of cardiovascular disease. Using *t*-test, the results were compared between the two groups.

Results: The prevalence of PD was high in patients with AMI (70.5%). AMI cases who had PD, showed significantly ($P < 0.05$) higher CRP levels (21.88 mg/l) than AMI patients without PD (9.26 mg/l). A positive relationship was observed between PD and serum CRP levels, and after matching all the potential confounders, PD emerged as a strong and independent predictor of elevated CRP levels.

Conclusion: Under the limitations of this study, periodontal disease was found to be common in patients with AMI and was associated with an enhanced inflammatory response, expressed by higher CRP levels. The relationship between PD and CRP levels in AMI patients appears to be independent of other contributing factors.

Key Words: Acute-phase proteins, Myocardial infarction, periodontal disease

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INTRODUCTION

Periodontal disease (PD) is a chronic, low-grade mixed bacterial infection involving the supporting structures of the teeth. This disease appears to be an important inflammatory stressor, causing increased hepatic synthesis of C-reactive protein (CRP), a recognized predictor of acute myocardial infarction (AMI) and stroke. The inflammatory process, can

involve the vasculature directly by interaction of the organisms or bacterial by-products with the vessel wall, or indirectly via modulation of haemostasis or hepatic activation of the acute phase response that leads to increased circulating levels of acute phase reactants such as C-reactive protein (CRP) [1-3].

Elevated CRP levels are associated with an increased risk for cardiovascular events in

healthy individuals and patients with known coronary artery disease. CRP has been shown to be not only a prognostic indicator of acute coronary syndromes, but also, a predictor of future coronary events. Perhaps the greater importance is the demonstration that CRP concentrations predict MI and stroke [4-6]. Therefore, identifying conditions that contribute to CRP level elevations may have significant prognostic and treatment implications in patients with cardiovascular disease. The aim of this cross-sectional study was to determine whether the presence of periodontal disease was associated with higher CRP levels in AMI cases.

MATERIALS AND METHODS

Study population

Based on a pilot study, 50 AMI patients were selected for the present study. Both patients with Q-wave AMI and non-Q-wave AMI were included. All participants were divided into two groups according to their periodontal health status. Potential confounders such as smoking, diabetes mellitus, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides (tg) and body mass index (BMI) were considered in the frequency matching between the two groups. Cases were also matched in terms of race and sex. AMI diagnosis was implemented based on more than 30 minutes of chest pain history accompanied by ischemic electro-cardiographic changes and confirmed by serial creatine kinase (CK) and CK-myocardial band level elevation tests. Active infection, being within 6 months of any periodontal surgical or non-surgical treatments, recent (<3 months) history of antibiotic use, and current corticosteroid therapy, constituted the excluding criteria. Only clinically stable patients, on whom a thorough oral examination could be performed within 72 hours post-symptom onset, were included in the study.

Periodontal examination

A thorough periodontal examination was carried out for sixty-two AMI patients within 72 hours of symptom onset, among which 51 cases were selected according to the determined study population.

Pocket probing depth (PPD) in 6 sites per tooth; bleeding on probing (BOP) in 4 sites per each of the 6 anterior teeth and clinical attachment level (CAL) in 6 sites per tooth were examined by a calibrated examiner and recorded. The severity of gingivitis was established as mild, moderate and severe on the basis of 1-30, 30-60, and >60% of sites having bleeding on probing. Periodontitis was considered as localized severe and generalized severe when less than 30% of the sites exhibited >4mm attachment loss and when at least 30% of the examined sites had >4mm attachment loss, respectively.

PD was considered to be a potential systemic exposure when >15% of the examined sites had a pocket depth of ≥ 4 mm. Because PPD represents a better marker of systemic inflammatory burden, each case status was assigned according to PPD; and every case showing this characteristic was included in the periodontal disease group. However all subjects meeting this definition underwent CAL measurements as well, to determine the disease extent and severity.

Laboratory tests

Samples were taken from patients at the time of symptom onset and between 24 and 72 hours from the onset of AMI. In doing so, serum confounders could be double-checked for adjusting. CRP was measured with high-sensitivity enzyme-linked immunosorbent assay (hs-ELISA), and values were expressed in milligrams per liter (mg/L).

Statistical analysis

Comparisons between AMI cases on the basis of presence or absence of PD were performed with standard *t*-test using SPSS software. Values are presented as means (SD). A P-

value of less than 0.05 was assumed to be significant.

RESULTS

From 62 periodontally examined patients, 11 cases were later excluded for different reasons; 4 cases because of antibiotic use, 5 for having BMIs over 27 kg/m², one with high fever, and one because of corticosteroid intake. Systemic metabolic conditions of the patients in two groups have no significant difference and are shown in Table I.

Thirty-six of the 51 participants had periodontal disease, which accounts for 70.5% overall periodontal involvement. At least 15% of the sites in the periodontal patients had more than 4mm PPD and attachment loss. From 36 patients, 31(86%) had moderate to severe generalized chronic periodontitis, and 5(14%) had moderate to severe localized chronic periodontitis. Although periodontally healthy AMI subjects seemed to be younger than periodontally diseased cases with AMI (50 versus 54), no statistical significant difference was found between two groups. Smokers were almost equally distributed among the two groups. The prevalence and severity of gingivitis among AMI cases is shown in Figure 1.

As expected, mean serum CRP levels were significantly (P<0.05) higher in patients with PD compared to subjects without periodontal disease (21.88 and 9.26 mg/l respectively). Meanwhile no statistical difference in CPK

Table I: Systemic metabolic condition of AMI patients in two studied groups.

	Patients without PD (n=15)	Patients with PD (n=36)
Age	50 (3)	54 (6)
Men%	71	78
HDL	42.06 (11.52)	40.8 (7.58)
LDL	146.93 (44.32)	143.44 (50.22)
Total	216 (48.42)	219 (57.75)
FBS	137.6 (56.8)	155.5 (63.6)

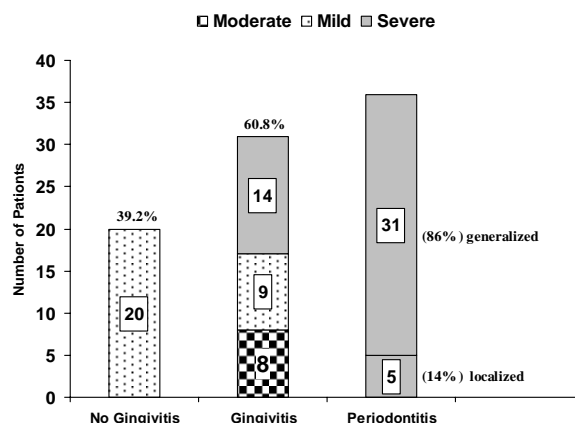


Fig. 1: Prevalence and severity of gingivitis and periodontitis among AMI patients.

was found between them, it was 1425.3 mg/l in patient without periodontal disease and 1410 mg/l in PD patients.

DISCUSSION:

The results from the current study showed that PD is quite common among AMI patients accounting for 70.5% of the studied cases. When present, PD is a powerful and independent contributor to elevated CRP levels. Efthymois et al [4] found a PD prevalence of 48% in patients with AMI compared to 17% in their control group of community volunteers without known heart disease. The higher prevalence rate in our study could be a result of the basic difference in the PD prevalence between the populations under investigation. A periodontal disease prevalence rate of 10-15% has been reported for the American general population [7], and although not comparable, the available CPITN data suggests a 22% periodontal involvement for individuals who reside in Guilan province, Iran [8]. The prevalence of PD in AMI patients in the present investigation (70.5%) was more than 3 times the common amount in the general population in the similar geographic area. A series of physiological or pathological conditions can be associated with periodontitis and coronary artery disease. Both disorders are

chronic multifactorial diseases that possibly share a series of etiological characteristics and factors, as a result of which both might coexist as a complex or syndrome [9]. Frequent features common to both diseases include male category, a low cultural status, habitual smoking and diabetes; though other clinical situations can not be excluded. Advanced age is a risk factor for both cardiovascular and periodontal diseases [10], however, in the present study, no statistically significant difference was found in mean age between AMI patients with or without periodontal disease. This would exclude the age dependent possibility of coincidence between periodontal and cardiovascular disorders.

The current investigation demonstrated that acute phase response, evidenced by elevated CRP levels is enhanced in AMI patients with PD. Results of this study, which is the first conducted among Iranian AMI patients, are consistent with previous reports showing increased rates of AMI in cases with elevated CRP levels [11-13]. A plausible biologic mechanism underlying the observed association between PD and cardiovascular events might be proposed.

Overall, there have been approximately 42 cross-sectional, case-control and longitudinal published studies that have examined the potential relationship between PD and cardiovascular disease (CVD), and 80% have shown significant positive associations. Among the 16 longitudinal studies, 10 have demonstrated that periodontal disease is significantly associated with an increased risk for cardiovascular events after adjustment for a variety of potential confounders [14]. Janket and Baird [15] performed a meta-analysis and concluded that a significant association exists between PD and CVD. The adjusted odds ratio (OR) was reported to be 2.85 for stroke, 1.19 for CVD, and 1.44 for cardiovascular events in subjects aged ≤ 65 years. Similarly, Meurman et al [16], in a meta-analysis of prospective

and retrospective follow-up studies have shown that PD may increase the risk of CVD by approximately 20% (95% confidence interval, ranged between 1.08-1.32). The reported risk ratio between PD and stroke was found to be even stronger.

The present study used a cross-sectional design and examined the presence of PD at the time of AMI. The observed elevation in CRP levels could be explained by the cascade of events caused by the invading oral flora during PD. A systemic response is triggered from the host, occurring as a prolonged persistent inflammatory up-regulation to the local, mixed gram-negative low-grade infection. Multiple studies have demonstrated a systemic inflammatory response and elevated CRP levels in adults with PD [3,4,17]. Ebersole et al [18] reported significantly higher levels of CRP among individuals with adult periodontitis, especially those having more active sites.

CRP levels have been proved to be useful in targeting therapy for primary and secondary prevention, as a screening tool for the assessment of cardiovascular risk in otherwise healthy populations, and also as an incremental and independent prognostic marker for recurrent coronary events among AMI patients. Therefore, identifying modulators of CRP production during an acute event may help distinguish patients who would most benefit from medications such as statins and aspirin [19,20]. In the present study, it has been demonstrated that the presence of PD as one of the modulators of CRP synthesis, increases the serum levels of CRP independent of infarct size, (as has been shown by the insignificant difference of CPK levels between the two groups) and other contributing factors. PD treatment modalities are classified as regenerative and reconstructive procedures, both of which must be attained by mechanical debridement including scaling and root planning. Local or systemic antibiotic therapy also improves the results and is recommended

for advanced and aggressive cases. After successful PD therapy there is a reduction in systemic levels of the acute phase proteins, including CRP [21,22].

CONCLUSION

Using careful and thorough periodontal examinations, the current investigation showed that PD was present in approximately two-third of the patients with AMI. Furthermore, PD contributed strongly to CRP level elevations which according to our data, was independent of other known contributing factors including the size of the infarction. Larger and multi-center trials incorporating a periodontal treatment arm are necessary to validate the high prevalence of PD in this population, and to examine possible benefits associated with its treatment. Since elevated CRP levels have been identified as a major risk factor for atherosclerotic and future cardiovascular events, it appears necessary to assess whether lowering its levels leads to a decrease in cardiovascular risk. In that case it can be implied that CRP is not merely a marker of risk, but is integrally involved in the etiologic mechanisms of cardiovascular disease.

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