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C-Reactive Protein is Associated with the Severity of Periodontal Disease — An Observational Study Among Acute Myocardial Infarction Patients

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ABSTRACT

Background — Acute myocardial infarction (AMI) is a continuous pathology characterized by inflammation as a leading etiopathogenesis, can cause morbidity globally. C-reactive protein (CRP) is produced by hepatic cells in response to inflammation; can be applied clinically as a wide-ranging inflammatory hallmark. Periodontal diseases (POD) are a prevalent, complex, insidious inflammation of the paradental supportive tissue. Recently, overwhelming evidence reinforced the bidirectional relation between POD and systemic disorders. Case in point, both POD and AMI intermingles within the equal inflammatory model. Our proposal was to perform a case-control study that could let us to evaluate the association between CRP and POD among AMI. **Patients and Methods** — This is a case-control study performed at cardiac catheterization center at Merjan teaching hospital, Babylon, Iraq. The studied sample of 136 patients with AMI aged between 29-89 years carefully chosen from the center attendance. All patients were examined orally for POD and examined for highly sensitive-CRP (HS-CRP), then compared with 76 healthy control. Grading of POD was executed based on ''a new classification outline for periodontial and preimplant diseases: Introduction and key changes from the 1999-classification''. While the severity of POD executed by using separate classical prob to estimate ''clinical-attachment-loss (CAL)'' separating the periodontium from the alveolar edge in millimeters.
Results — Periodontal status was significantly worse in AMI patients. As well, HS-CRP were elevated significantly in this group. No gender and mean BMI alterations among the two groups. Higher incidence of tobacco smoke, diabetes and hypertension were observed among AMI patients. Higher mean HS-CRP values, rates of hypertension and tobacco smoke among male participants were detected. The study revealed a high significant association between high levels of HS-CRP with diabetes. Thus far, just positive no significant association between high levels of HS-CRP with hypertension among studied patients. A positive direct association between POD (in terms of both severity and grading) and HS-CRP among AMI patients (P-0.00), were noticed. **Conclusions** — In patient with AMI, higher HS-CRP levels are definitely associated with severity of POD. Patients with AMI has a higher HS-CRP levels compared to healthy controls.

Keywords:

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INTRODUCTION

During contemporary years, innovative discoveries have renewed our knowledge about the biology of acute myocardial infarction (AMI). AMI is a chronic progressive disorder that could be a reason for morbimortality universally [1,2,3,4]. In the pathogenesis of AMI, the persuasive inflammatory role of coronary-vessels is well documented [5, 6].C-reactive protein (CRP) is a general ''acute-phase-reactant'' formed by liver in response to inflammation; used as a general biomarker for systemic and vaso-inflammation [7, 8]. The later effect might be due to local production by atheroma and vascular smooth cells [9]. Periodontal diseases (POD) are a prevalent, complex, insidious inflammation of the paradental supportive tissue, commenced as bacterial biofilm then ensued mostly by disturbed host immunity and progressing loss of attaching gingiva [10,11].

METHODOLOGY

Study design and Patients

This case-control study enrolled 136 patients diagnosed as AMI and 74 healthy controls. Participants collected from those attending Shahidul-Mihrab center at Merjan teaching hospital of Babylon. All study members completed medical and oral examination and signing an informed consent formula. The plasma analysis of HS-CRP was conducted at the central laboratory of the hospital. All study events are in line with the moralities of the Helsinki-Declaration. The study agreed by the Ethical Committee of the Babylon health directorate.

Assessment of Severity of Periodontal Diseases:

An expert examiner completed oral inspection using a specific mirror and tooth-explorer. Grading of POD was executed based on ''a new classification outline for periodontial and preimplant diseases: Introduction and key changes from the 1999-classification'' [12]. While the severity of POD executed by using separate classical prob to estimate ''clinical-attachment-loss (CAL)'' separating the periodontium from the alveolar edge in millimeters (mm) [13, 14, 15].

Grouping of Study Participants

Patients were divided into three grades of POD: normal periodontium, localized POD, and generalized POD. Moreover, the severity of POD in patients was subdivided according to CAL into four stages: healthy or normal gum (less than 2mm), mild POD (2-3mm), moderate POD (4-5mm) and sever POD when CAL was more than 5mm.

Analysis of Highly sensitive C-reactive protein

The levels of HS-CRP were analyzed at the day of hospitalization were assessed by a high sensitivity immunoturbidometric assay using immunology analyzer (Roche Diagnostics®), Cobas c111- USA.

Statistical Analysis

The continuous parameters were displayed as mean±SD, while categorical parameters as (frequency and percentage). Compared percentage of the presence or absence of risk factors across the groups were finalized with *chi-square* correlation test. Associations between HS-CRP level and POD (stages and grades) were examined by *linear*-regression. The ''Cronbach's-Alpha-reliability test'' of survey variables was more than 0.94. Statistical investigates were achieved using SPSS/23-IBM, with a significance-value designed at 0.05.

RESULTS

Characteristics of the Parameters of the Study

The mean ages of AMI patients more than healthy group (59.3 vs 39.5 years) individually. The study exposed that patients with AMI exhibited poor periodontal state. The later issue reflected by significantly higher stages and grades of POD among AMI patients than in controls [apart from grade-1 or mild POD which was more frequent among the controls]. The levels of HS-CRP were significantly higher among AMI patients (p-0.05). Both mean BMI measures and distribution of gender were equivalent among the two groups. As predictable, the AMI subjects had significantly (p-0.05) more incidence of risk factors in terms of smoking, hypertension and diabetes than in healthy control (table-1). Independent T-test used to investigate gender distribution of POD, which revealed no impact of gender on both severity and stages of POD among studied participants (results not shown).

Correlation of HS-CRP with Diabetes Mellitus and Hypertension

In table-2, compared to healthy subjects; a positive highly significant correlation observed between HS-CRP and diabetes (*p*-0.024) among patients with IHD. Meanwhile, positive-correlation between HS-CRP and diabetes was observed among patients, although not reach significant level (p-0.26).

Table-1: Basic group characteristics differences between 136 patients with acute myocardial infarction and 74 healthy control

Characteristics	Total (210)	CAD patients (N=136)	Healthy control (N=76)	Significance
Age	52.3±16.1	59.3±13.8	39.5±11.3	0.05
Female sex	38	29 (76.3%)	9 (23.7%)	NS
BMI (Kg/m2)	28.3±5.0	27.2±5.0	26.7±0.4	NS
Smoking		54 (39.7%)	18 (24%)	0.05
Grades of Periodontal diseases				
Normal (No %)	62	47 (75.8)	15 (24.2)	0.001
Mild (No %)	81	24 (29.6)	57 (70.4)	0.001
Moderate (No %)	38	3 (79)	35 (92.1)	0.001
Sever (No %)	29	0	29 (100)	0.001
Stages of Periodontal Diseases				
Normal (No %)	59	47 (20.3)	12 (79.7)	0.001
Localized (No %)	24	7 (70.8)	17 (29.2)	0.001
Generalized (No %)	117	97 (82.9)	20 (17.1)	0.001
HS-CRP (mg/L)	4.7±6.1	8.2±6.7	1.1±0.7	0.05
Diabetes mellitus (No %)	67	59 (43.4)	8 (10.8)	0.001
Hypertension (No %)	73	68 (50)	5 (6.8)	0.001

Table-2: Correlation of highly sensitive CRP to diabetes mellitus and hypertension in IHD and healthy control

Diabetes Mellitus	Coronary artery diseases				Healthy control			
	Grades of HS-CRP			*P-value*	Grades of HS-CRP			*P*-value
	Low	Moderate	High		Low	Moderate	High	
Present no (%)	3 (10.0)	4 (13.3)	23 (76.7)	0.024	3 (37.5)	5 (62.5)	0	0.28
Absent no (%)	1 (2.2)	1 (2.2)	43 (95.6)		39 (59.1)	25 (37.9)	2 (3.0)	
Hypertension								
Present no (%)	1 (2.9)	2 (5.9)	31 (91.2)	0.26	4 (80)	1 (20)	0	0.26
Absent no (%)	3 (7.3)	3 (7.3)	35 (85.4)		38 (55.1)	29 (42.0)	2 (2.9)	

Correlation of HS-CRP and Periodontal Status

There was a positive significant association between mean HS-CRP levels with grades of POD (P-0.00) among all study subjects (figure-1). Whereas, positive but, weak association of mean HS-CRP levels with stages of POD (figure-2).

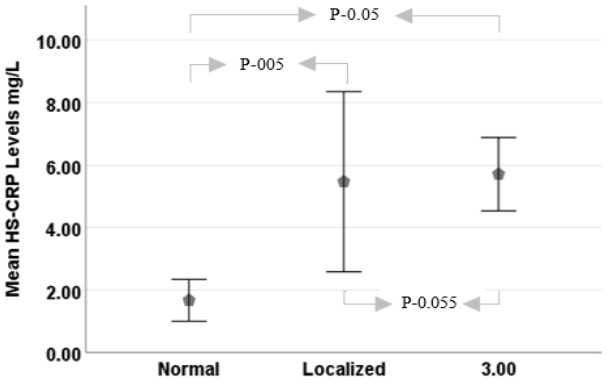

Figure-2: Correlation of Mean HS-CRP Levels According to Stages of Periodontal Diseases Among Studied Subjects

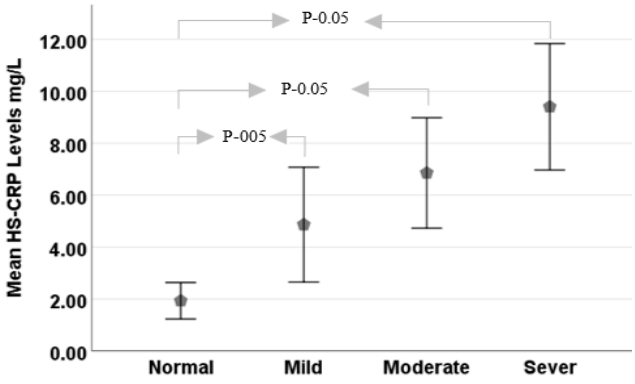

Figure-1: Correlation of Mean HS-CRP Levels with Grading of Periodontal Diseases Among Study Subjects

The values gained from the *ROC*-curve (figure-3); revealed that the optimum cut off point for HS-CRP (above which a subject gets risk of AMI) in defining AMI is 2.78 mg/L. The true positives (sensitivity) at this cut off is 0.895 (89.5%) and false positives (1-specificity) is 0.91 (9.1%).

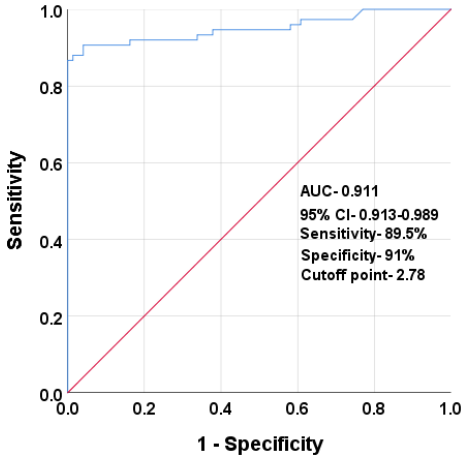

Figure-3: ROC curve predictability of HS-CRP for acute myocardial infarction

DISCUSSION

In this study, the question under discussion is the association of higher levels of HS-CRP with POD among patients with AMI. There is overwhelming evidence corroborating the concept of a significant correlation between poor oral hygiene and AMI [4,16,17,18]. Thus far, the specific biomechanism of such links remains a matter of argument [19]. Nevertheless, inflammation might be one of the most significant shared pathology between AMI and oral health [16,17,20]. The bioactivity of oropathogens in arteriosclerosis, hyperlipidemia, besides higher protease-activated-receptors could be added probable explanations [21,22]. After adjusting the impacts of confounders like age, gender, and smoke habits; a significant correlation between POD and AMI recognized by our former work [21]. Similarly a current two surveys in Babylon exposed same outcomes [16, 23]. The authors in this article assume that in patients with AMI a probable linkage between HS-CRP and POD may be exist. The existing results provide confirmatory evidence that one of the most vital locations of CRP synthesis is the periodontium [9]. In patients with AMI, POD may confound the usual progression of the sclerotic event thereby increases risk for plaque vulnerability. A vulnerable-plaque is a plaque that is mostly insecure for higher risk of rupture, that may prompts an AMI [24].

In POD, local immune response to oropathogenic flora or its products is characterized by access of inflammatory elements, WBCs, and plasma cells, into the periodontium [25]. Cytokines released from activated macrophages are involved in gum destruction and trigger acute response that includes CRP, whose raise has been recognized as a shared element for both POD and AMI [3,12]. These findings are consistent with the outcomes of this work in terms of higher HS-CRP levels observed among patients with AMI and among those with worse grades and stages of POD. In the same strain, other studies showed that POD elevates the systemic concentrations of HS-CRP, that lead to higher inflammatory response in the coronary-lesions, and possibly increasing the risk for cardiovascular events [26].

This article presents the claim that sex showing no effects on the study parameters, except the rates of smoking, hypertension and values of HS-CRP. As predicted, males

have a tendency to have all smoke products more than females [27]. Above and beyond, sex differences in hypertension were obvious; females were far less predominant [28,29]. To finish, significant gender differences observed in the levels of CRP amongst the population in several studies [30].

The similar mean BMI values in both groups were probably due to controls were collected from same families and associates of the AMI patients recruited in the study. A closer look at the data indicates that a positive significant relation between HS-CRP and diabetes in patients, despite the positive nonsignificant relation between HS-CRP and hypertension. In this respect, our conclusions be in accord with some other works [19, 31, 32]. On the contrary, in many previous surveys, the unfavorable diabetic effects on the gum have not been proven [33]. Of note, diabetes had an effect on both gum health and levels of CRP mutually [34]. Revisions have publicized that CRP is higher in diabetic patients compared to controls [35,36]. Then again, other scholars reported no relation between CRP and diabetes [37]. Partway, raised CRP levels in diabetic patients may be due to obesity and higher BMI [38], or might be attributed to increased predisposition of diabetics to infections besides diabetes problems [35, 39]. Worth mentioning, diabetics are susceptible for AMI, the increased CRP levels -partly- might reflect the inflammatory component of atherogenesis that is so common among diabetics [40].

The accurate physiology that correlating hypertension with POD are uncertain. Inflammatory response disrupted collagen uptake, and oxidative stress, are plausible associations. Hypertension-associated inflammatory process may exaggerate the host immunity to oropathogenic flora, with eventual periodontal damage [41].

In this article, a higher levels of CRP have correlated with increased risk of myocardial infarction, which might coincide the role of enduring inflammation in AMI [42]. Existing conclusions suggest that elevated CRP may be just as dynamic as rising low density lipoproteins (LDL) levels in predicting AMI [43]. CRP enhances the progress of atherogenesis due to its proinflammatory activities, modulation of innate-immunity and complements series, platelets activation, along with vascular remodeling [4]. Moreover, CRP enhances LDL consumption by macrophage cells and its capability to form ''foam-cells''. As well, CRP also hampers the endothelial expression of NO synthase which has important anti-thrombogenic effects [44]. Moreover, CRP rises PAI-1 (protease-inhibitor), which controls fibrinolysis, thus leads to atherogenesis [45].

I am not alone in my view that HS-CRP is associated significantly with both POD and AMI. Several other investigators , fair to name a few, have all displayed a analogous relations in their trials as well [33,46, 47, 48].

The data generated by this paper revealed that the optimal cutoff for HS-CRP (over which a subject has risk of AMI) in defining AMI was reported to be 2.78 mg/L. This cutoff value was estimated from the ROC analysis. Upon such outcomes it can be supposed that HS-CRP is not just a risk factor but likewise a risk predictor as well, similar to our previous results [2,4, 8]. To give the main points of this paper, current research seems to validate the view that POD has a strong association with the systemic inflammation in AMI patients. The precise mechanism correlating these threesome (i.e. HS-CRP, POD, and AMI) might be further clarified with future clinical and epidemiological studies.

CONCLUSION

The study outcomes may lead to these conclusions; in patient with AMI, higher HS-CRP levels are definitely associated with severity of POD. Patients with AMI has a higher HS-CRP levels compared to healthy controls.

LIMITATIONS

Amongst the limitations of our study, we highpoint the unfeasibility, for practical and economic reasons, of executing inflammatory biomarker detection and hematological recognition of bacterial agents of POD. Henceforth, random clinical trials including greater numbers of AMI patients and concurrent study of other risk biomarkers – inflammatory, genomic, and hematological - can increase our data for a better spotting of the contribution of inflammation in the progression of acute thrombotic events.

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