Relationship between high-sensitivity C-reactive protein serum levels and the severity of coronary artery stenosis in patients with coronary artery disease

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Original Article

Abstract

BACKGROUND: High-sensitivity C-reactive protein (hs-CRP) inflammatory biomarker is one of the best informative markers of prognosis of coronary artery disease (CAD) that has been studied. Some studies have found that hs-CRP has a direct correlation with CAD. The aim of this study was to determine the relationship between serum levels of hs-CRP and the severity of coronary artery stenosis in patients with stable and unstable angina.

METHODS: In a cross-sectional study, 150 patients undergoing coronary angiography in Golestan Hospital Ahvaz, Iran in 2012, were studied in three groups of stable angina (n = 50), unstable angina (n = 50), and normal coronary angiography (n = 50). Hs-CRP levels were measured in patients before angiography by enzyme-linked immunosorbent assay method, were compared between the three groups and its correlation with the degree of stenosis was evaluated.

RESULTS: The mean levels of hs-CRP in the stable angina group, unstable angina group and the group with normal coronary angiography were 2.46 ± 1.79, 4.84 ± 3.38, and 2.95 ± 2.57 mg/L, respectively. The results show that the mean levels of hs-CRP in patients with unstable angina was significantly higher compared to patients with stable angina ($P < 0.050$) and patients with normal coronary angiography ($P < 0.001$). However, a statistical difference between the mean CRP levels in patients with stable angina and patients with normal angiography results was not seen ($P > 0.050$). A significant relationship between arterial stenosis points and hs-CRP levels in patients with stable angina was not seen ($P = 0.985$).

CONCLUSION: The findings suggest that it seems hs-CRP level in patients with unstable angina were significantly higher than those in patients with stable angina and patients with normal coronary angiography. It also appears that the level of hs-CRP in patients with unstable angina is associated with the severity of coronary stenosis. Given the finding of consistent results, the use of hs-CRP as a prognostic factor in these patients may be useful.

Keywords: Coronary Artery Disease, High-sensitivity C-reactive Protein, Stable Angina, Unstable Angina

Date of submission: 31 Aug 2014, ***Date of acceptance:*** 27 July 2016

Introduction

Coronary artery disease (CAD) is one of the leading causes of mortality in the world.[1,2] CAD is the most common form of cardiovascular disease with a prevalence of 6.9% in men and 6% in women. It is currently the leading cause of morbidity and mortality in people older than 38 years in Iran. Death from heart disease in this country ranges from 28% to 48%, and the incidence of ischemic heart disease is highly reported.[3] Studies show that risk factors for cardiovascular disease may differ in different societies. Even in cases where the relationship between these risk factors and CAD among different populations appears to be identical, the prevalence of these risk factors may differ, as the prevalence rate in Iran has been reported differently than in other countries.[4,5] Many risk factors for cardiovascular disease can be regulated by specific preventive measures.[6,7] These risk factors include smoking, dyslipidemia, hypertension,

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diabetes, abnormal obesity, lack of daily consumption of fruits and vegetables, regular alcohol consumption, and lack of regular physical activity.[8,9] Although other factors such as older age and male gender are listed as risk factors for CAD, these factors alone cannot predict the relative risk of the disease and the discovery of new markers may help identify patients at risk.[10,11] Because atherosclerosis is the main focus of CAD researchers, the study of the factors influencing the process of atherosclerosis is highly valuable. Fundamental research shows that inflammation is involved in all stages of the process of atherosclerosis[12,13] and is followed by clinical complications. Furthermore, inflammation is the main initiator of plaque formation and plays a role in incomplete endothelial function, plaque instability, and plaques rupture.[14,15] High-sensitivity C-reactive protein (hs-CRP) is one of the best studied inflammatory biomarkers in CAD.[16,17] Hs-CRP, a marker of systemic inflammation, rises in response to injury, infection, and other inflammatory stimuli.[18,19] Unlike other inflammatory phase reactants, serum hs-CRP remains high for a long time, even in the absence of stimuli.[20-22] Furthermore, a number of studies have shown a stable relationship between hs-CRP levels and an increased risk of cardiovascular events such as myocardial infarction and cardiovascular death.[23-26] However, the mechanisms responsible for the association between hs-CRP and cardiovascular disease remain unclear.[27] Although some studies have found that hs-CRP was poorly correlated with the severity of CAD, other studies have suggested a strong association between hs-CRP and the severity of stenosis.[28,29] On the other hand, less attention has been paid to the relationship between hs-CRP, the activation of plaque and the incidence of unstable angina, and warnings of hs-CRP for ischemic events. Therefore, the aim of this study was to determine the relationship between serum levels of hs-CRP and the severity of coronary artery stenosis in patients with stable and unstable angina.

Materials and Methods

A total of 150 patients undergoing coronary angiography participated in this cross-sectional study in Educational Governmental Golestan Hospital, Ahvaz city, Khuzestan, South West of Iran, in 2012. Among all of patient that visited during 2012, 150 patients (that have stable or unstable form of angina, without any inflammatory diseases or any immunosuppresses drug and have not any problem to test serum levels of hs-CRP) obtained randomly in this study. Written informed consent from all participants and approval from the Ethics Committee of the Medical University of Ahvaz was obtained. Patients with a history of infectious disease, connective tissue disease, acute myocardial infarction, heart failure, left ventricular ejection fraction < 30%, smoking, surgery 3 months before the study, and factors affecting the level of CRP were excluded from the study.

Questionnaires including questions about age, gender, history of hypertension, history of diabetes, and dyslipidemia were completed. The patients' blood pressure and pulse rate were measured while resting. The electrocardiogram was gathered from all patients. Furthermore, the level of white blood cells, blood sugar, triglycerides, cholesterol, and blood creatinine were each measured and recorded in Hospital Laboratory, glucose oxidase test, and cholesterol oxidase-peroxidase, respectively. Before angiography, 5 ml of venous blood sample was taken from fasting patients. The samples were transported to the laboratory, where hs-CRP levels were measured by enzyme-linked immunosorbent assay. Coronary angiography was performed by Judkins method. To determine the degree of stenosis genesis scoring was performed in which eight major coronary vessels including left main, left anterior descending, diagonal, first septal, left circumflex coronary artery, obtuse marginal, patent ductus arteriosus, and right coronary artery were studied. The degree of stenosis was reported on a scale from 0 to 4, with 0 meaning no narrowing, Grade 1 stenosis of < 50%, Grade 2 stenosis of 50-75%, Grade 3 stenosis of 75-99% and Grade 4 was considered as complete obstruction. Based on this method vessels can achieve a score of 0-32. Patients were divided into three groups of 50 persons that were enrolled consecutively: patients with stable angina who have angiographic lesions (Group I), patients with unstable angina who had angiographic lesions (Group II), and patients with stable or unstable angina who had normal coronary angiographies (Group III).

According to previous studies[28] and the formula, 150 patients entered in three groups. For describing data, the mean and standard deviation were used. The primary assumption of normality was checked using Kolmogorov–Smirnov test. The nonsignificant results of this test ($P = 0.198$, $P = 0.124$) suggesting no violation of the assumption of normality for hs-CRP and severity of coronary stenosis. Hence, both variables appear to

be reasonably normally distributed. The chi-square goodness of fit test was used to test whether all categories contain the same proportion of values. One-way analysis of variance (ANOVA) followed by Tukey multiple comparison tests was utilized to compare the means of hs-CRP and severity of coronary stenosis among the three groups. The relationship between hs-CRP level and arterial stenosis was investigated using Pearson product-moment correlation coefficients. Statistical analysis was performed using IBM SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY, USA). A statistically significant result is one in which the observed P value is < 0.05.

Results

Out of 150 patients examined in this study, 50 patients had unstable angina, 50 patients had stable angina, and 50 patients had normal angiograms. 61 of the participants were male and 89 were female. The mean age for male participants was 56.6 ± 10.6 and the mean age for female participants was 55.5 ± 12.4 years, which did not have a statistically significant difference ($P = 0.577$). In addition, 37.7% of men and 46.1% of women had hypertension, 32.8% of men and 34.8% of women suffered from dyslipidemia, and 29.5% of men and 40.4% of women had Type II diabetes, of which, none showed statistically significant differences ($P = 0.115$, $P = 0.468$ and $P = 0.198$, respectively) in three groups.

As shown in table 1, the male to female ratios were 0.28, 1.38, and 0.72 for normal angiography, stable angina, and unstable angina groups, respectively, where showed a statistically significant difference ($P < 0.001$).

The percentages of patients with hypertension were 34%, 42%, and 52% for normal angiography, stable angina, and unstable angina groups, respectively. The percentages of patients who suffered from dyslipidemia were 32%, 40%, and 30% in three groups, respectively. In normal angiography group, 24% had Type II diabetes. Moreover, 42% of patients in stable angina group and 36% of patients in unstable angina groups had Type II diabetes.

A chi-squared test was conducted to test whether three categories contain the same proportion of patients. The results indicated that there were not statistically significant differences between the proportion of patients with hypertension, dyslipidemia, and Type II diabetes in unstable angina, stable angina, and normal angiography groups ($P = 0.190$, $P = 0.536$, $P = 0.096$).

Furthermore, the mean hs-CRP level and vasoconstriction amount were evaluated based on gender, hypertension status, dyslipidemia and diabetes, of which hs-CRP levels and vasoconstriction amount only showed significant differences between the two gender groups. ($P < 0.001$) (Table 2).

Table 2 showed the mean and standard deviations for hs-CRP, and severity of coronary stenosis for patients in normal angiography, stable angina, and unstable angina groups. The results are presented as mean ± standard deviation (SD).

A one-way ANOVA was done to see whether there are significant differences between the mean of hs-CRP levels and severity of coronary stenosis among three groups. Primary assumption testing was conducted to check for normality and homogeneity of variance. The results showed that the two assumptions were met. The results of ANOVA test indicated a statistically significant difference in the mean of the CRP levels among three groups ($P < 0.001$). The results of Tuckey pairwise comparison tests showed that the mean of CRP level for unstable angina group was significantly higher than the other two groups ($P < 0.001$). However, the results did not show a statistically significant difference between the mean of hs-CRP levels in patients with stable angina and patients with normal angiograms ($P > 0.050$). The ANOVA test also revealed that there was not a statistically significant difference in the mean severity of coronary stenosis among the three groups. As depicted in table 2, the same results were obtained where the analysis was separately conducted on male and female patients.

Table 1. Patients' characteristics

Characteristics	Normal angiography	Stable angina	Unstable angina	Total	P
Number of patients	50	50	50	150	-
Male: female raito	0.28 (11.39)	1.38 (29.21)	0.72 (21.29)	0.68 (61.89)	< 0.001
Patients with hypertension (%)	17.00 (34.00)	21.00 (42.00)	26.00 (52.00)	64.00 (42.70)	0.190
Patients with dyslipidemia (%)	16.00 (32.00)	20.00 (40.00)	15.00 (30.00)	51.00 (34.00)	0.536
Patients with Type II diabetes (%)	12.00 (24.00)	21.00 (42.00)	18.00 (36.00)	51.00 (34.00)	0.096

Table 2. Comparison of high-sensitivity C-reactive protein (hs-CRP) and severity of coronary stenosis among normal angiography, stable angina and unstable angina groups

Variable	Normal angiography		Stable angina		Unstable angina		P
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
hs-CRP level							
Male	11	3.09 ± 2.05	29	2.90 ± 2.14	11	6.25 ± 4.14	< 0.001
Female	39	2.91 ± 2.73	11	1.85 ± 0.84	29	3.82 ± 2.28	< 0.001
Total	50	2.95 ± 2.57	50	2.46 ± 1.79	50	4.84 ± 3.38	< 0.001
Severity of coronary stenosis							
Male	11	-	29	12.28 ± 4.90	11	10.05 ± 4.51	0.108
Female	39	-	11	8.95 ± 6.28	29	9.07 ± 4.47	0.939
Total	50	-	50	10.88 ± 5.70	50	9.48 ± 4.47	0.663

hs-CRP: High-sensitivity C-reactive protein; SD: Standard deviation

Furthermore, the mean hs-CRP level and vasoconstriction amount were evaluated based on gender, hypertension status, presence of dyslipidemia and diabetes, of which the mean of hs-CRP levels and vasoconstriction amount only showed significant differences between the two gender groups ($P < 0.001$).

The relationship between hs-CRP level and arterial stenosis was investigated using Pearson product-moment correlation coefficients. Preliminary analyses were performed to ensure no violation of the assumptions of normality and linearity. As shown in table 3, for unstable angina group, a correlation coefficient of 0.518 indicates that there was a significant moderate linear relationship between hs-CRP level and severity of arterial stenosis ($P < 0.001$). In addition, the correlation coefficient of 0.105 showed that there was not a significant linear relationship between hs-CRP level and arterial stenosis for stable angina group ($P = 0.958$).

Table 3. Correlations between high-sensitivity C-reactive protein (hs-CRP) level and arterial stenosis in stable angina and unstable angina groups

Variable	N	Correlation coefficient (r)	P
Stable angina			
Male	29	0.114	0.887
Female	21	0.101	0.960
Total	50	0.105	0.922
Unstable angina			
Male	21	0.531	< 0.001
Female	29	0.509	< 0.001
Total	50	0.518	< 0.001

hs-CRP: High-sensitivity C-reactive protein

Since this study was designed to determine, whether, an increase in one variable caused an increase in the value of a second variable it would seem logical to say that in unstable angina, severity of coronary stenosis is more likely to increase when hs-CRP increases.

Discussion

The previous studies suggest an association between serum hs-CRP levels and cardiovascular disease.[30-32] However, in these studies, the predictive potential of hs-CRP on cardiovascular events has been studied, but the degree of arterial stenosis or the relationship with arterial lesion type has not been vastly evaluated.[33-35] The results of this study suggest that hs-CRP levels in patients with coronary artery lesions and unstable angina were higher compared to patients with stable angina and patients with normal angiograms. A significant difference was not seen between the serum levels of hs-CRP in patients with stable angina and patients with normal coronary angiography. Although this statistical relationship was present in all CAD patients, later analysis showed that this relationship is simply due to the linear relationship between hs-CRP levels and vasoconstriction points in patients with unstable angina and this relationship was not seen in patients with stable angina. The results of previous studies are consistent with our findings. In 2011 in India, Masood et al. studied 80 patients in a similar study which also showed a statistically significant relationship between hs-CRP levels and the extent of vascular stenosis.[36] Furthermore, Assadpour Piranfar et al.,[37] in 2012, in a study titled evaluation of serum hs-CRP with the severity of vascular stenosis showed that levels of hs-CRP in patients with moderate and severe stenosis was significantly more than patients with mild stenosis. Consistent results were also found in a study of Luo[38] in 2010 in China. The results of their study also showed that there was a significant relationship between the serum levels of hs-CRP and severity of

coronary stenosis. In our study and the three previously mentioned, the relationship between serum hs-CRP levels and the severity of CAD was assessed using the Gensini score and comparison of the same variables with the same index in the above studies indicate the results of these studies are consistent. Another strength of this study was a large sample size compared to other studies. Moreover, patients were studied in three groups: patients with stable angina, patients with unstable angina, and patients with normal coronary angiographies. Furthermore, the mean hs-CRP level and vasoconstriction points were evaluated based on predisposing factors such as hypertension status, dyslipidemia, and diabetes. Similar studies with opposite or conflicting results are inevitable in the field of research therefore, some studies with conflicting results have also been found. For example, in a study by Avanzas et al.,[29] in 2004 in London, the relationship between hs-CRP levels and the severity of coronary stenosis showed that a significant relationship between arterial stenosis points and hs-CRP levels in patients with stable angina was not seen. Another study conducted in Iran by Kojouri et al.[27] in 2010 also suggest that a significant correlation between serum hs-CRP levels and the degree of stenosis in patients with stable angina was not seen. The lack of consistent results in different studies can be due to many reasons. One of these reasons can be the assessment of patients in different research communities or the genetic susceptibility of individuals. In this study, the mean serum hs-CRP level and arterial stenosis in male participants were higher than in female participants. In a study by Kojouri et al.,[27] mean serum hs-CRP levels in male participants with stable angina was higher than in female participants. The baseline hs-CRP is an important factor in the outcome of the research. The median hs-CRP level is 1.5-2.2 mg/dl.[39] But in our study, the overall mean hs-CRP level in patients was 2.84 ± 3.42, 2.95 ± 2.57 mg/l in the normal angiography group, 2.46 ± 1.79 mg/l in the stable angina group and 4.84 ± 3.38 mg/l in the unstable angina group, which shows the high biodiversity of hs-CRP. In this study, patients' medications, their habits and diet, level of physical activity, body mass index and body fat distribution was not considered. As these factors could also influence the results of the study, it is recommended that they be addressed in future studies. It seems hs-CRP level in patients with unstable angina were significantly higher than those in patients with stable angina and patients with normal coronary angiography. It also appears that the level of hs-CRP in patients with unstable angina is associated with the severity of coronary stenosis. Other studies with a larger volume of patients, consideration of contributing factors and multiple hs-CRP measurement is recommended.

Acknowledgments

This study is the result of thesis number d/534 from Ahvaz Jundishapour University of Medical Sciences. The authors would like to thank all colleagues who contributed to this study and the Golestan Clinical Research Development unit especially Ms. Caroline Kheradmand for English translation and editing of this paper.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Seyedian SM, Ahmadi F, Dabagh R, Davoodzadeh H**. Relationship between high-sensitivity C-reactive protein serum levels and the severity of coronary artery stenosis in patients with coronary artery disease.** ARYA Atheroscler 2016; 12(5): 231-7.