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C-reactive protein and coronary calcium score association in coronary artery disease

Ali Hosseinsabet[1], Ahmad Mohebbi[2], Alireza Almasi[3]

[1]Tehran, Iran
[2]Department of Cardiology, Shaheed Rajaei Cardiovascular Center, Iran University of Medical Sciences, Tehran, Iran
[3]Department of Radiology, Shaheed Rajaei Cardiovascular Center, Iran University of Medical Sciences, Tehran, Iran

Abstract

Background: *Both high-sensitivity C-reactive protein (hs-CRP) and spiral computed tomography coronary artery calcium score (CCS) are valid markers of cardiovascular risk. It is unknown whether hs-CRP is a marker of atherosclerotic burden or whether it reflects a process leading to acute coronary events.*

Methods and Results: *We studied the relation between hs-CRP and CCS in 143 patients that were candidates for coronary artery bypass grafting (CABG). In our cross-sectional study, we found no significant association between hs-CRP and CCS in bivariate ($p = 0.162$) and multivariate ($p = 0.062$) analysis, but in patients who did not use statins this association was positive and significant in bivariate analysis ($p = 0.001$), and in multivariate analysis this association was negative and significant ($p = 0.008$).*

Conclusions: *High-sensitivity CRP was not correlated with CCS. The relation between CRP and clinical events might not be related to atherosclerotic burden. Measures of inflammation, such as hs-CRP, and indices of atherosclerosis, such as CCS, are likely to provide distinct information regarding cardiovascular risk.* (Cardiol J 2008, 15: 431–436)

Key words: coronary calcification, inflammation, risk factors, multislice spiral computed tomography, high-sensitivity C-reactive protein

Introduction

A great deal of evidence suggests that inflammation plays a major role in the development of atherosclerosis and its clinical manifestations [1, 2]. In some studies, plasma levels of inflammatory markers, particularly high-sensitivity C-reactive protein (hs-CRP), predict myocardial infarction and cardiovascular death [3–8]. However, hs-CRP is associated with many established risk factors including dyslipidemia, cigarette smoking, hypertension, diabetes and obesity [9–15]. The relation between hs-CRP and coronary artery disease (CAD) was positive and significant in some studies [16–18], in other studies this relation was not significant [17, 19–27] and in others it was negative and significant [28, 29]. The extent to which hs-CRP levels predict clinical events depends on the relation of hs-CRP to the burden of underlying atherosclerosis or the milieu leading to plaque rupture and thrombosis, and is unknown. Given that hs-CRP levels predict clinical events, it is of great interest to dissect

Address for correspondence: Ali Hosseinsabet, Department of Cardiology, Shaheed Rajaei Cardiovascular Center, Vali-e-asr Avenue, Tehran, Iran, tel: +98 (21) 23922580, fax: +98 (21) 22055594, e-mail: ali_hosseinsabet@yahoo.com
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the pathophysiology of this relation. In contrast to clinical events, an independent association between hs-CRP levels and coronary [19–29] or carotid [27, 30–36] atherosclerosis has not been established clearly. Coronary artery calcification (CAC), measured by electron beam tomography (EBT) or spiral computed tomography, might be useful in identifying novel risk factors for coronary atherosclerosis in asymptomatic subjects. The amount of CAC at EBT is correlated with the burden of atherosclerosis at both autopsy and coronary angiography [37, 38] and studies suggest that CAC is a predictor of clinical CAD events in both symptomatic [39] and asymptomatic [40, 41] subjects. Studies of CAC might permit differentiation of factors associated with coronary atherosclerosis from those related to plaque rupture or thrombosis.

Studies of hs-CRP and CAC in healthy subjects have produced conflicting results. Whereas some have found no association between hs-CRP and CAC [17–29], others have reported a weak relation [16–18]. It is unclear whether these conflicting reports reflect the limitations of study design and analysis or real differences in the pathophysiology of CAC, a measure of coronary atherosclerotic burden, and elevated hs-CRP, a marker of inflammation.

Some support the concept that coronary calcium scores (CCS) and plasma hs-CRP levels might provide independent and complementary information regarding the risk of cardiovascular events [22, 42].

We examined the association between plasma hs-CRP and CCS in patients that were candidates for coronary artery bypass grafting (CABG). In previous studies, the subjects of studies were suspected to have CAD without any documentation, but in our study we selected patients who had CAD documented by selective coronary artery angiography.

Methods

Study population

The study population consisted of 143 patients with coronary artery disease that were admitted to the Shaheed Rajaei Cardiovascular Center, an academic tertiary referral center, between December 2006 and March 2007 for CABG. When the patients were admitted to our centre for CABG, their history was taken and physical examinations were carried out.

Exclusion criteria were:

— history of myocardial infarction or unstable angina during previous month;
— history of aortic valve replacement or mitral valve replacement;
— history of CABG or coronary stenting.

All study participants gave written informed consent. The protocol was approved by the Research Committee at the Iran University of Medical Sciences, Tehran. Age, cardiac risk factors including hypertension, dyslipidemia, diabetes mellitus, family history of coronary disease, smoking status and drug history were determined by interview (self-reported), and body mass index (BMI) by examination.

Biochemical data determination

Blood sampling was done for lipid profile, creatinine [43–45] and hs-CRP, and the blood samples were frozen at –70°C for four months. The hs-CRP was done using commercial kits (Pars Azmun Co.), by latex immunoturbid assay (detection limit was 0.1 to 10 mg/L and coefficient variation was 1%) and by a single laboratory technician blinded to all clinical and radiological data.

Coronary calcium score determination

Coronary calcium scoring was done by 10-slice spiral computed tomography scan (Siemens Somatom Sensation 10). The calcium score of coronary artery was expressed according to the work of Agatston and colleagues [46]. A total CAC score was determined from the sum of the individual scores of the four major epicardial coronary arteries. A single radiologist, blinded to all clinical and serologic data, interpreted all scans.

Statistical analysis

The data were analyzed by SPSS 15 software and reported as mean ± standard deviation (SD) if continuous, and as proportions if categorical. Because some variables did not have normal distribution, we transformed them to logarithmic values for normalization of data, and because some patients had CCS=0, log (CCS+1) was substituted. Firstly, we assessed the association between coronary calcium score log (CCS+1) and log (hs-CRP) overall by Pearson correlation coefficient and then in the presence of age, sex, any risk factors and any drugs use by this method. Because almost all patients used aspirin and beta-blockers, and a very small percentage of patients used calcium channel blockers or gemfibrozil, we did not include these variables in our analysis. Secondly, we assessed this correlation by multivariable linear regression (enter mode) overall, and then, in accordance with statin usage, we entered age, BMI, drug history, all risk factors, lipid profile and creatinine in multivariable analysis.

Table 1. Characteristics of the study sample.

Age (years)	57.7 ± 9.4
< 50	18.2
50–59	39.2
60–69	30.8
> 70	11.9
Body mass index [kg/m^2]	27.2 ± 3.5
< 24.99	29.4
25–29.99	49
> 30	21.6
Triglycerides [mmol/L]	1.73 ± 0.88
Cholesterol [mmol/L]	4.46 ± 1.27
LDL cholesterol [mmol/L]	4.43 ± 0.81
HDL cholesterol [mmol/L]	1.06 ± 0.98
Creatinine [mmol/L]	121.1 ± 84
hs-CRP [mg/L]	2.89 ± 3.43
Coronary calcium score	366.4 ± 586.7
Male	74.1
Hypertension	32.2
Dyslipidemia	45.5
Diabetes mellitus	32.9
Cigarette smoking	35
FH	14
ACEI/ARB	51.7
Statins	62.2

*Values are mean ±SD, or percent; LDL — low density lipoprotein, HDL — high-density lipoprotein, hs-CRP — high sensitive C-reactive protein, FH — family history of coronary artery disease, ACEI/ARB — angiotensin converting enzyme inhibitors/angiotensin receptor blockers

Table 3. Correlation of log (hs-CRP) and log (CCS+1) in all cases and subgroups.

Group	r	p
Male	0.122	0.213
Female	0.037	0.828
Hypertension (+)	0.144	0.339
Hypertension (–)	0.118	0.248
Dyslipidemia (+)	0.091	0.469
Dyslipidemia (–)	0.136	0.236
Diabetes mellitus (+)	0.176	0.236
Diabetes mellitus (–)	0.096	0.353
FH (+)	0.101	0.673
FH (–)	0.101	0.267
Cigarette smoking (+)	0.144	0.318
Cigarette smoking (–)	0.110	0.296
ACEI/ARB (+)	0.091	0.442
ACEI/ARB (–)	0.132	0.281
Statin (+)	0.006	0.958
Statin (–)	0.442	0.001
Age (years)		
< 50	0.140	0.944
50–59	0.110	0.420
60–69	0.327	0.031
> 70	0.333	0.192
Body mass index [kg/m^2]		
< 24.99	0.100	0.528
25–29.99	0.080	0.632
> 30	0.323	0.081
All cases	–0.118	0.162

(+) indicates the presence of the condition and (–) indicates the absence of the condition; FH — family history of coronary artery disease, ACEI/ARB — angiotensin-converting enzyme inhibitors/ /angiotensin receptor blockers

Results

Table 1 shows the demographic characteristics, hs-CRP levels and CCS scores in the sample (n = = 143). Distribution of CCS is presented in Table 2.

Bivariate analysis of the correlation of hs-CRP and CCS in all patients and subgroups are presented in Table 3. This correlation was not significant overall (r = –0.118, p = 0.162) but was significant in 60–69-year-old patients (r = 0.327, p = 0.031), and these correlations were moderate and significant in patients that did not use statins (r = 0.442, p = 0.001). In other subgroups, this correlation was not significant. Factors associated with CCS when hs-CRP was not included in fully adjusted, multivariable linear regressions are shown in Table 4. Age, male sex and family history of coronary artery disease were positive predictors of CCS.

Factors associated with CCS when hs-CRP was included in fully adjusted, multivariable linear regressions are shown in Table 5. Age was the only predictor of CCS in the presence of hs-CRP; sex and family history of coronary artery disease were not predictors of CCS after adjustment for hs-CRP levels. Because, in bivariate analysis, the association of hs-CRP and CCS was significant in patients who did not use statins, we analyzed this association in these patients using fully adjusted,

Table 2. Percentiles of coronary calcium score (CCS) in the sample.

Percentiles	10	20	30	40	50	60	70	80	90
CCS	3.1	15.9	41.5	85.3	124.5	198.7	399.2	646.6	1107.0

Table 4. Multivariate analysis of factors associated with coronary calcium score when high-sensitivity C-reactive protein (hs-CRP) is not included in analysis.

	B	SD	P
(Constant)	1.173	1.323	0.377
Age	0.034	0.008	0.000
Sex	–0.409	0.191	0.035
Hypertension	0.304	0.177	0.089
Dyslipidemia	0.019	0.163	0.909
Diabetes mellitus	0.121	0.165	0.464
FH	0.470	0.212	0.028
Cigarette smoking	0.058	0.172	0.735
ACEI/ARB	–0.069	0.153	0.651
Statin	–0.146	0.157	0.355
LDL	0.000	0.003	0.859
Log HDL	0.138	0.184	0.455
Log TG	–0.182	0.159	0.257
Log CR	–0.134	0.252	0.598
Body mass index	–0.014	0.021	0.514

Results of linear regression [log (CCS+1) as the dependent variable] presented when log hs-CRP is not included in the analysis, as the change log (CCS+1) for a specific change in risk factor. The model was adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease (FH), smoking, use of the following medications: statins, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), LDL (log LDL), HDL (log HDL), TG (log TG), CR (log CR), body mass index; CR — creatinine; TG — triglycerides

Table 5. Multivariable analysis of factors associated with coronary calcium score when high-sensitivity C-reactive protein (hs-CRP) is included in analysis.

	B	SD	P
(Constant)	1.046	1.312	0.427
Age	0.037	0.008	0.000
Sex	–0.343	0.193	0.078
Hypertension	0.293	0.176	0.099
Dyslipidemia	–0.005	0.161	0.977
Diabetes mellitus	0.141	0.164	0.392
FH	0.395	0.213	0.067
Cigarette smoking	0.068	0.170	0.688
ACEI/ARB	–0.032	0.153	0.834
Statin	–0.204	0.158	0.200
LDL	0.001	0.003	0.657
Log HDL	0.089	0.184	0.630
Log TG	–0.169	0.158	0.288
Log CR	–0.063	0.253	0.802
Body mass index	–0.013	0.021	0.542
Log hs-CRP	–0.115	0.061	0.062

Results of linear regression [log (CCS+1) as the dependent variable] presented when log hs-CRP is included in analysis as the change log (CCS+1) for a specific change in risk factor. The model was adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease (FH), smoking, use of the following medications: statins, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), LDL (log LDL), HDL (log HDL), TG (log TG), CR (log CR), body mass index and hs-CRP (log hs-CRP); CR — creatinine; TG — triglycerides

Table 6. Multivariable analysis of factors associated with coronary calcium score high-sensitivity C-reactive protein (hs-CRP) in patients that did not use statins.

	B	SD	P
(Constant)	3.774	1.682	0.031
Age	0.021	0.012	0.088
Sex	–0.653	0.262	0.017
Hypertension	0.318	0.259	0.227
Dyslipidemia	0.086	0.243	0.724
Diabetes mellitus	0.250	0.226	0.276
FH	0.682	0.318	0.038
Cigarette smoking	–0.346	0.275	0.215
ACEI/ARB	0.191	0.231	0.414
LDL	0.004	0.004	0.294
Log HDL	0.188	0.219	0.396
Log TG	–0.261	0.241	0.285
Log CR	–0.531	0.292	0.077
Body mass index	–0.068	0.037	0.077
Log hs-CRP	–0.278	0.100	0.008

Results of linear regression [log (CCS+1) as the dependent variable] are presented in patients who did not use statins, as the change log (CCS+1) for a specific change in risk factor. The model was adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease (FH), smoking, use of the following medications: statins, angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), LDL (log LDL), HDL (log HDL), TG (log TG), CR (log CR), body mass index and hs-CRP (log hs-CRP); CR — creatinine; TG — triglycerides

multivariable linear regression. Table 6 shows this analysis. Male sex and family history of coronary artery disease were positive predictors of CCS, and hs-CRP was a negative predictor of CCS ($p = 0.008$) in patients who did not use statins.

Discussion

Traditionally, the risk of a clinical coronary event reflects the burden of underlying coronary atherosclerosis, factors that lead to plaque rupture and factors that promote thrombus formation. Coronary artery calcification is strongly associated with total plaque burden, as proven in histopathological studies. The amount of CAC at EBT is correlated with the burden of atherosclerosis at both autopsy and coronary angiography [37, 38] and preliminary studies suggest that CAC is a predictor of clinical CAD events in both symptomatic [39] and asymptomatic subjects [40, 41]. Studies of CAC might permit the differentiation of factors associated with coronary atherosclerosis from those relating to plaque rupture or thrombosis. CCS, measured by spiral computed tomography, might be useful for exploring the relation of risk factors with

coronary atherosclerosis. We found no evidence of a positive association between hs-CRP and calcium scores. Indeed, if anything, these data suggest an inverse relationship between hs-CRP levels and coronary calcium in patients who did not use statins. Nonetheless, we believe the lack of a positive association between hs-CRP and coronary calcium score deserves careful consideration. The lack of correlation in the current data between spiral computed tomography CCS and hs-CRP suggests that calcification may be less likely to reflect inflammation per se; spiral computed tomography detected calcification may predominantly be a marker for mature, and hence stable, atherosclerotic plaque, and thus only be an indirect marker for the presence of uncalcified rupture-prone lesions, which may be more likely markers for future cardiac events. However, a correlation between soft, noncalcified plaque and hs-CRP has not been confirmed [24].

Deposition of calcium in atherosclerotic lesions has been shown to be an active process analogous to the formation of bone spicules [47]. Thus, coronary calcification may not merely be a direct consequence of atherogenesis but may depend upon the presence of specific determinants independent of the central processes involved in plaque formation. Our finding supports the concept that hs-CRP levels might not be related to atherosclerosis but may be a marker of plaque rupture and thrombosis. Therefore, hs-CRP might not be useful in identifying the underlying mechanisms of atherosclerosis initiation or progression.

We used a validated commercial assay for the measurement of hs-CRP, but variability in commercial assays may limit the validity of these data. We used CCS as a surrogate for coronary atherosclerotic plaque burden based on the well-established relationship between CCS and the extent of histological plaque [37]. However, atherosclerosis in vascular beds other than the coronary arteries could also contribute to the level of hs-CRP [48].

Conclusions

This study demonstrates that hs-CRP is unrelated to the presence and severity of clinical calcified atherosclerosis, and suggests that serologic inflammatory markers are principally a measure of the atheroinflammatory disease process and are not an index of the extent of coronary atherosclerotic plaque. Because CCS and hs-CRP are associated with risk of subsequent cardiovascular events, these two measures may be complementary rather than competitive for risk prediction.

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