C - Reactive Protein and Coronary Calcium Score Association in Coronary Artery Disease

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Abstract

Objectives- Both high-sensitivity C-reactive protein (hs-CRP) and spiral computed tomography coronary artery calcium score 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- We studied the association of high-sensitivity C-reactive protein and coronary calcium score in 143 patients that were candidates for coronary artery bypass graft surgery.

Results- In our cross sectional study we found no significant association between high-sensitivity C-reactive protein and coronary calcium score in bivariants (p=0.162) and multivariable (p=0.062) analysis, but in patients who did not use statins, this association was significant and positive in bivariant (p=0.001) and in multivariant analysis this association was negative and significant (p=0.008).

Conclusion- High-sensitivity C-reactive protein was not associated with coronary calcium score. The relation between C-reactive protein and clinical events might not be related to atherosclerotic burden. Measures of inflammation, such as C-reactive protein, and indices of atherosclerosis, such as coronary calcium score, are likely to provide distinct information regarding cardiovascular risk ***(Iranian Heart Journal 2009; 10 (1):40-47).***

Key words: coronary calcification ■ C-reactive protein ■ inflammation ■ atherosclerosis ■ risk factors

Much evidence exists to suggest 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 C-reactive protein (CRP), predict myocardial infarction and cardiovascular death.[3-8] However, CRP is associated with many established risk factors, including dyslipidemia, cigarette smoking, hypertension, diabetes and obesity[9-15] and the relation between CRP and coronary artery disease (CAD) has been significant in some studies,[16-18] but in others it has not been significant[17,19-27] and has even been significantly negative in others.[28,29]

The extent to which CRP levels predict clinical events depends on the relation of CRP to the burden of underlying atherosclerosis or the milieu leading to plaque rupture and thrombosis, and is unknown. Given that CRP levels predict clinical events, it is of substantial interest to dissect the pathophysiology of this relation. In contrast to clinical events, an independent association between 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.

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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 CRP and CAC in healthy subjects have produced conflicting results. While some studies have found no association between 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 CRP, a marker of inflammation.

Some support the concept that CAC scores and plasma CRP levels might provide independent and complementary information regarding the risk of cardiovascular events.[22,42]

Methods

The study population comprised 143 patients with coronary artery disease admitted to our center, an academic tertiary referral center, from December 2006 to March 2007 for coronary artery bypass graft (CABG) surgery. When patients were admitted to our center for CABG, medical history and physical examination were completed and patients were excluded from study if they had a history of the following conditions:

1-myocardial infarction or unstable angina during the previous month,

2-aortic valve replacement or mitral valve replacement surgery,

3- CABG surgery or coronary stenting.

All study participants gave written informed consent. The protocol was approved by the Research Committee of 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. Blood sampling was done for lipid profile, creatinine[44-46] and hs-CRP and frozen at -70° C for four months. Hs-CRP measurement was done by commercial kits (Pars Azmun Co.), by latex immunoturbid assay and by a single laboratory technician blinded to all clinical and radiologic data. Routine lab data included lipid profile and creatinine, and coronary calcium scoring was done by 10-slice spiral CT scan (Siemens Somatom Sensation 10). Calcium score of the coronary arteries was expressed according to Agston et al.,[43] as previously explained. A total CAC score was determined from the sum of individual scores of the 4 major epicardial coronary arteries. All scans were interpreted by a single radiologist blinded to all clinical and serologic data.

Data were analyzed by SPSS 15 software and reported as mean ± SD if they were continuous and as proportions if they were categorical.

Because some variables did not have normal distribution, we transformed them to logarithmic 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 any risk factors and any drug use in both sexes by this method.

Because almost all patients used aspirin and beta- blockers, and a negligible percents of patients used calcium channel blockers or gemfibrozil, we did not include them in our analysis. Secondly, we assessed this correlation by multivariable linear regression (enter mode) overall and then according to statins use.

We entered age, BMI, drug history, all risk factors and lipid profile and creatinine in the multivariate analysis.

Results

Table I shows demographic characteristics, CRP levels, and CCS scores in the sample (n=143). Bivariant analysis of CRP and CCS in all patients and subgroups is presented in Table II.

Table I. 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
BMI, kg/m2	27.2± 3.5
<24.99	29.4
25-29.99	49
>30	21.6
Tg, mg/dl	153.6± 78.2
Cholesterol, mg/dl	171.4± 48.8
LDL, mg/dl	94.0 ±31.4
HDL, mg/dl	41.0± 37.9
CR, mg/dl	1.37± 0.95
hs-CRP, mg/dl	2.89± 3.43
CCS	366.4± 586.7
Male	74.1
HTN	32.2
DLP	45.5
DM	32.9
C/S	35
FH	14
ACEI/ARB	51.7
Statins	62.2

Values are mean±SD, or percent. BMI=body mass index, Tg=triglyceride, LDL=low density lipoprotein, HDL= high density lipoprotein, CR=creatinine, hs-CRP=high sensitivity CRP, CCS=coronary calcium score, HTN=hypertension, DLP=dyslipidemia, DM=diabetes mellitus, C/S=cigarette smoking, FH=family history of coronary artery disease, ACEI/ARB=angiotensin converting enzyme inhibitor/ angiotensin receptor blocker

This correlation w as not significant overall (r=-0.118, P=0.162), and was significant in 60-69 year-old patients (r =0.327, P=0.031) and in patients who did not use statins (r=0.442, P=0.001), this correlation was moderate and significant. In other subgroups this correlation was not significant. Table III shows factors which were associated with CCS, when C - reactive protein is not included in a fully adjusted multivariable linear regression. Age, male sex and family history of coronary artery disease were positive predictors of CCS.

Table II. 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
HTN (+)	0.144	0.339
HTN (-)	0.118	0.248
DLP (+)	0.091	0.469
DLP (-)	0.136	0.236
DM (+)	0.176	0.236
DM (-)	0.096	0.353
FH (+)	0.101	0.673
FH (-)	0.101	0.267
C/S (+)	0.144	0.318
C/S (-)	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 <50	0.140	0.944
50-59	0.110	0.420
60-69	0.327	0.031
>70	0.333	0.192
BMI <24.99	0.100	0.528
25-29.99	0.080	0.632
>30	0.323	0.081
ALL CASES	-0.118	0.162

* (+) is presence of the condition and (–) is absence of the condition.

Table III. Multivariate analysis of factors associated with coronary calcium score when C-reactive protein is not included in the 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
HTN	0.304	0.177	0.089
DLP	0.019	0.163	0.909
DM	0.121	0.165	0.464
FH	0.470	0.212	0.028
C/S	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
LogHDL	0.138	0.184	0.455
LogTG	-0.182	0.159	0.257
LogCR	-0.134	0.252	0.598
BMI	-0.014	0.021	0.514

*Results of linear regression (log of (CCS+1) as the dependent variable) are presented when CRP is not included in analysis, as the change log(CCS+1) for a specific change in risk factor. Models were adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease, smoking, use of the following medications: statins, ACEI/ARB ,LDL[log LDL] ,HDL[logHDL], TG[logTG] ,CR[logCR], body mass index.

Factors which were associated with CCS, when C - reactive protein is included in the fully adjusted multivariate linear regression are shown in Table IV. Age was the only predictor of CCS in the presence of CRP, and sex and family history of coronary artery disease were not predictors of CCS after adjustment for CRP level.

Table IV. Multivariable analysis of factors associated with coronary calcium score when C- reactive protein is included in the 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
HTN	0.293	0.176	0.099
DLP	-0.005	0.161	0.977
DM	0.141	0.164	0.392
FH	0.395	0.213	0.067
C/S	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
LogHDL	0.089	0.184	0.630
LogTG	-0.169	0.158	0.288
LogCR	-0.063	0.253	0.802
BMI	-0.013	0.021	0.542
LogCRP	-0.115	0.061	0.062

*Results of linear regression (log of (CCS+1) as the dependent variable) are presented when CRP is included in analysis as the change log(CCS+1) for a specific change in risk factor. Models were adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease, smoking, use of the following medications: statins, ACEI/ARB ,LDL[log LDL] ,HDL[logHDL] TG[logTG] ,CR[logCR], body mass index and CRP [logCRP].

Because in bivariant analysis the association of log (CRP) and log (CCS+1) was significant in patients who did not use statins, we analyzed this association in patients in fully adjusted, multivariate linear regression. Table V shows this analysis. Male sex and family history of coronary artery disease are positive predictors of CCS, and CRP was negative predictor of CCS (P=0.008) in patients who did not use statins.

Table V. Multivariable analysis of factors associated with coronary calcium score and C - reactive protein in patients not using 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
HTN	0.318	0.259	0.227
DLP	0.086	0.243	0.724
DM	0.250	0.226	0.276
FH	0.682	0.318	0.038
C/S	-0.346	0.275	0.215
ACEI/ARB	0.191	0.231	0.414
LDL	0.004	0.004	0.294
LogHDL	0.188	0.219	0.396
LogTG	-0.261	0.241	0.285
LogCR	-0.531	0.292	0.077
BMI	-0.068	0.037	0.077
LogCRP	-0.278	0.100	0.008

*Results of linear regression (log of (CCS+1) as the dependent variable) are presented in patients that not use statin, as the change log (CCS+1) for a specific change in risk factor. Models were adjusted for the following variables; age, sex, history of hypertension, history of dyslipidemia, diabetes mellitus, family history of coronary artery disease, smoking, use of the following medications: statins, ACEI/ARB ,LDL[log LDL] ,HDL[logHDL] ,TG[logTG] ,CR[logCR], body mass index and CRP [logCRP]

Discussion

CCS measured at spiral CT might be useful for identifying novel risk factors and exploring the relation of risk factors with coronary atherosclerosis. We have examined the association between plasma CRP and CCS in patients who were candidates for CABG. In previous studies, subjects of the study were suspected to have coronary artery disease without any documentation as proof, but in our study we selected patients who had coronary artery disease documented and confirmed by selective coronary artery angiography. 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 CT score and hs-CRP suggests that calcification may be less likely to reflect inflammation per se; spiral CT-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, but a correlation between soft, noncalcified plaque was not confirmed.[24] Deposition of calcium in atherosclerotic lesions has been shown to be an active process analogous to the formation of bone spicules. [47] Furthermore, it appears to involve cells of special embryonic lineage.

Thus, coronary calcification may not merely be a direct consequence of atherogenesis but rather may depend upon the presence of specific determinants independent of the central processes involved in plaque formation. The reasons for the lack of association between CRP and CCS, in contrast to a more consistent association between CRP and clinical events, are unclear. However, this finding supports the concept that CRP levels might not be related to atherosclerosis per se, distinct from being a marker of plaque rupture and thrombosis. Therefore, CRP might not be useful in identifying the underlying mechanisms of atherosclerosis initiation or progression. The present findings suggest that the relationship between higher CRP levels and incident cardiovascular events may reflect the composition, morphology, and stability of plaque rather than overall atherosclerotic burden.[48] Because CCS are associated with risk for subsequent cardiovascular events and provide a measure of disease processes distinct from CRP, these two measures may be complementary rather than competitive for risk prediction. [42]

This study, demonstrating that hs-CRP is unrelated to the presence and severity of clinical calcified atherosclerosis, suggests that serologic inflammatory markers are principally a measure of the athero-inflammatory disease process and are not an index of the extent of coronary atherosclerotic plaque. The independent prognostic utility of quantifying calcified atherosclerosis and systemic inflammation suggests that disease and process markers of atherosclerosis may be complementary tools in coronary heart disease prediction.

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 on the basis of the well-established relationship between CCS and the extent of histologic plaque.[37] However, atherosclerosis in vascular beds other than the coronary arteries could also contribute to the level of hs-CRP.[49]

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Conflict of Interest

No conflicts of interest have been claimed by the authors.

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