Evaluation of C-Reactive Protein, Fibrinogen and Antithrombin-III as Risk Factors for Coronary Artery Disease

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Abstract

Background: Inflammation is an important feature of atherosclerotic lesions and increased production of the acute-phase reactant. The contribution of coagulation factor to the development of coronary artery disease has not yet been clearly established.

Objectives: To test whether C-reactive protein, fibrinogen and antithrombin-III are associated with angiographic CAD, history of myocardial infarction and extensive atherosclerotic involvement.

Methods: Blood samples were tested for CRP, fibrinogen and AT-III levels from 219 individuals undergoing coronary angiography.

Results: CRP was higher in patients with CAD (0.95 ± 1.31, n = 180, vs. 0.39 ± 0.61 mg/dl, n = 39, $P < 0.0001$) and in those with a history of MI (1.07 ± 1.64, n = 96, vs. 0.65 ± 0.72 mg/dl, n = 84, $P < 0.05$) than in control subjects. The patients who developed unstable angina had higher CRP levels than the patients with stable CAD (2.07 ± 2.38, n = 7, vs. 0.80 ± 1.13 mg/dl, n = 173, $P < 0.001$). Fibrinogen was significantly higher in patients with CAD than in those without CAD (298 ± 108 vs. 258 ± 63 mg/dl, $P < 0.01$). In patients with CAD, mean AT-III value was less than in patients without CAD, but this difference was not statistically significant ($P = 0.08$). No difference was found in CRP, fibrinogen and AT-III values among the patients with single, double or triple vessel disease.

Conclusions: CRP is elevated in patients with CAD and a history of MI. Elevated levels of CRP at the time of hospital admission is a predictive value for future ischemic events. There is an association between higher levels of fibrinogen and CAD. The association of AT-III levels with CAD needs testing in further studies.

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CAD = coronary artery disease
CRP = C-reactive protein
AT-III = antithrombin-III
MI = myocardial infarction

Epidemiological studies have shown a significant association between several risk factors, such as smoking, hypertension, dyslipidemia, diabetes mellitus, and the pathogenesis of coronary atherosclerosis. Currently, several new risk factors – namely elevated levels of lipoprotein(a), homocysteinemia, elevated levels of plasminogen activator inhibitor, excessive iron load in the body, an imbalance between oxidant and antioxidant species, and angiotensin-converting enzyme polymorphism – are being described in atherosclerosis [1–6]. Furthermore, experimental and clinical studies have provided evidence for the presence of ongoing inflammation in atherosclerosis [7,8]. In addition, new data suggest that bacterial, parasitic or viral infection may initiate the inflammatory process [9].

C-reactive protein and fibrinogen are easily measurable and highly sensitive acute-phase reactants that are synthesized in response to pro-inflammatory cytokines, such as interleukin-6, which is the major determinant of acute-phase protein production [10]. Increased concentrations of CRP appear to be predictive of higher risk for coronary events in patients with stable and unstable angina, as well as in asymptomatic patients at risk for coronary artery disease [11,12]. It has been suggested that fibrinogen, which plays a pivotal role in the coagulation cascade, is an independent cardiovascular risk factor [13]. Moreover, antithrombin-III, which is an inhibitor of thrombin and of factor Xa, may have an important etiologic role in the prognosis of patients with angina pectoris [14]. Therefore, in this study we investigated the value of serum levels of CRP, fibrinogen and AT-III in patients with stable angina undergoing coronary angiography.

Methods

Patient population

The study population consisted of 219 consecutive patients who had suspected or known CAD and were scheduled for coronary angiography [Table 1]. To support the presence of ischemic heart disease, patients must have met at least one of the following criteria: a history of typical myocardial ischemic-type discomfort, electrocardiographic changes (ST segment deviation or T wave inversion, or both) in association with ischemic discomfort, a previous positive exercise test, reversible ischemia at myocardial perfusion imaging, a history of previous myocardial infarction, a

Table 1. Clinical and angiographic characterictics of study patients

	Patients (n = 219)	
	No.	%
Age (yr)	58	10
Male	147	67%
Systemic hypertension	109	49%
Diabetes mellitus	38	17%
Hypercholesterolemia	29	13%
Cigarette smoking	96	43%
Family history of CAD	44	20%
Previous MI (> 3 months)	96	
Anterior	50	
Inferior	31	
Non-Q	15	
Patients with CAD	180	82%
Single vessel disease	94	
Double vessel disease	45	
Triple vessel disease	41	
Patients without CAD	39	18%

previous coronary angiography showing 50% stenosis of a major epicardial coronary vessel, previous coronary angioplasty, or coronary artery bypass graft surgery. Exclusion criteria were: unstable angina, acute MI within 3 months, inflammatory conditions likely to be associated with an acute-phase response (such as fever, increased level of leukocytes, chronic infection and inflammatory diseases), chronic significant hepatic, pulmonary or renal diseases, and neoplastic disease. At the time of coronary angiography, all patients were on oral aspirin and isosorbide dinitrate.

Blood sampling

Peripheral blood samples for measurement of CRP, fibrinogen and AT-III were taken from an antecubital vein after admission to hospital, before the coronary angiography and without any intravenous drug administration.

Laboratory assays

C-reactive protein and AT-III were assayed by an automated nephelometric immunoassay using a Beckman Array instrument (Beckman Array 360 system, Canada). Fibrinogen was measured using a photo-optic method on the Organon Technica Durham Coa-A instrument (Organon Technica, North Carolina, USA).

Coronary angiography

The procedure was performed using standard coronary catheters via the femoral route. We defined a patient as having CAD if there was any angiographic evidence of atherosclerosis, excluding < 20% stenoses or any luminal wall irregularity of the epicardial coronary tree. A patient was defined as being free of CAD if all coronary arteries were judged to be angiographically smooth. All patients were observed for 48 hours after the coronary angiography, before hospital discharge. In the period between coronary angiography and hospital discharge, a patient was considered to have unstable angina if there was recurrence of new resting chest pain associated with transient ECG signs of myocardial ischemia.

Statistical analysis

The statistical analysis was performed using the Statistical Package for Social Sciences software (SPSS for Windows). Continuous variables were compared using *t* tests for paired and unpaired variables, as appropriate. Proportions were compared using the chi-square test. The variables are expressed as mean standard deviation; *P* values < 0.05 were considered statistically significant.

Results

Patient groups

Clinical and angiographic characteristics are summarized in Table 1. Of the 219 study subjects, 180 (82%) had evidence of CAD ranging from > 20% to significant stenoses by coronary angiography. The remaining 39 patients whose coronary arteries were judged to be angiographically smooth were defined as being free of CAD. Patients with CAD and those without CAD did not otherwise differ significantly in cardiovascular risk factors. Altogether 96 patients (43%) had had previous MI. There were 94 (52%) patients with single-vessel disease among the patients with CAD, and of these patients 64 (68%) had left anterior descending disease, 18 (19%) had circumflex disease, and 12 (13%) had right coronary artery disease.

CRP, fibrinogen, AT-III levels in patients with CAD

Mean CRP and fibrinogen values were significantly higher in patients with CAD compared to those without CAD ($P < 0.0001$ and $P < 0.01$, respectively). Elevated levels of CRP were found to be an important risk factor for CAD. In patients with CAD, mean AT-III value was less than in patients without CAD, but this difference was not significant statistically ($P = 0.08$) [Table 2].

CRP, fibrinogen, AT-III levels in patients with history of MI or unstable angina

In patients who had previous MI, the CRP value was significantly higher than in patients without previous MI, as shown in Figure 1 (1.07 ± 1.64 vs. 0.65 ± 0.72 mg/dl, $P < 0.05$, respectively), whereas fibrinogen and AT-III values were not different between these two subgroups (295 ± 112 vs. 285 ± 93 mg/dl, $P > 0.05$ and 27.71 ± 3.52 vs. 27.54 ± 3.72 mg/dl, $P > 0.05$, respectively). Furthermore, in the subgroup of patients with chest pain associated with transient ECG signs of myocardial

Table 2. Levels of CRP, fibrinogen, AT-III in patients with and without CAD

	Patients with CAD	Patients without CAD	*P* value
CRP (mg/dl)	0.95 ± 1.31	0.39 ± 0.61	< 0.0001
Fibrinogen (mg/dl)	298 ± 108	258 ± 63	< 0.01
AT-III (mg/dl)	27.39 ± 3.62	28.47 ± 3.48	= 0.08

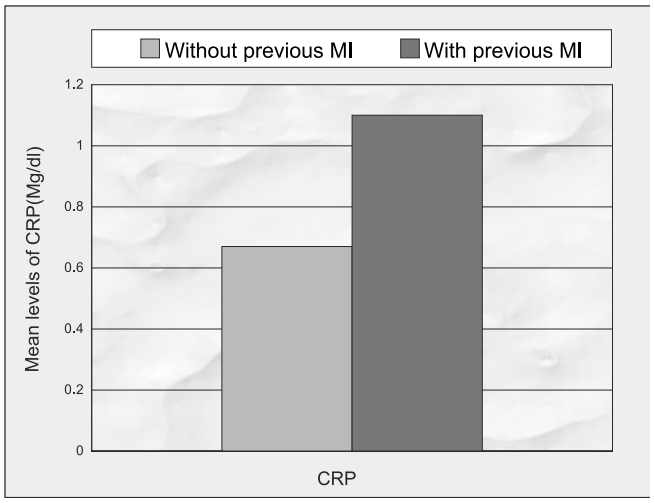

Figure 1. Mean levels of CRP in patients without previous MI and with previous MI. $P < 0.05$.

ischemia before discharge (7 patients), CRP was found to be significantly higher than in patients without any evidence of ischemia (2.07±2.38 vs. 0.80±1.13 mg/dl, $P < 0.001$, respectively). There was no difference between these two subgroups regarding fibrinogen and AT-III (348±128 vs. 289±103 mg/dl, $P > 0.05$ and 25.35±4.93 vs. 27.65±3.58 mg/dl, $P > 0.05$, respectively).

Relationship between CRP, fibrinogen, or AT-III levels and extensive CAD

No difference was found in CRP, fibrinogen and AT-III values among the patients with single, double or triple vessel disease (CRP levels 0.95±1.57, 0.87±1.02, 1.11±0.95; fibrinogen levels 296±107, 303±117, 296±99; AT-III levels 27.51±3.78, 27.55±3.44, 26.95±3.47, all $P > 0.1$, respectively). However, in the 94 patients with single vessel disease, including LAD, CX and RCA disease, CRP was significantly higher in patients with LAD disease than with CX or RCA disease (all $P < 0.05$). There was no difference between CX and RCA disease for CRP. In addition, no difference was observed among LAD, CX and RCA disease for fibrinogen and AT-III [Table 3].

Discussion

In this study, we demonstrated an association between elevated levels of CRP and CAD. The association was marked (twofold elevation) and highly significant ($P < 0.0001$). CRP concentration was also strongly associated with history of MI ($P < 0.05$) and future unstable angina, which could be observed during the hospital period after the coronary angiography ($P < 0.001$). Also, our findings suggested that the increased levels of fibrinogen were positively correlated with CAD ($P < 0.01$), but not with history of MI and future unstable angina. There was a weaker positive relation with decreased levels of AT-III and CAD ($P = 0.08$), and no relation with AT-III levels and history of MI, nor future unstable angina.

Table 3. Levels of CRP, fibrinogen, AT-III in patients with single vessel disease considering lesion localization

	LAD disease	CX disease	RCA disease
CRP (mg/dl)	**1.11**±1.83	0.52±0.51*	0.52±0.51*
Fibrinogen (mg/dl)	288±100	308±119	318±134
AT-III (mg/dl)	26.90±3.71	28.34±3.76	29.42±3.74

* $P < 0.05$ vs. CRP level of LAD.

Inflammation is an important feature of atherosclerotic lesions and increased production of the acute-phase reactants. During the atherosclerotic process the presence of local inflammatory response with monocytes, macrophages and T lymphocytes in the arterial wall has been increasingly recognized and documented [8,15]. Release of key cytokines, such as interleukin-6, result in stimulation of hepatic production of acute-phase reactants [16]. Thus, acute-phase reactants have been proposed as a potential indicator of underlying atherosclerotic disease. C-reactive protein and fibrinogen are highly sensitive and widely measurable acute-phase reactants [10].

C-reactive protein and fibrinogen have been found to be elevated in patients with CAD. Mendall et al. [12] reported elevated levels of CRP in patients with CAD, and Anderson et al. [17] reported more than twofold elevations of CRP in patients with CAD compared with control subjects without CAD. In the Scottish Heart Health Study [18], fibrinogen was found to be an important risk factor for CAD in men and woman, with and without pre-existing CAD. The published results from a meta-analysis have indicated a significant association between CAD and increased levels of both fibrinogen and CRP [19]. These results are compatible with our findings. AT-III as a risk factor has hardly been investigated until now. Thompson et al. [14] reported a negative relation between the risk of cardiac events and AT-III level. Similarly, we found lower AT-III levels in patients with CAD, but it was not statistically significant ($P = 0.08$).

Studies have supported the association between CRP or fibrinogen and an increased risk of cardiac events. In the Physicians Health Study [20], the increased level of CRP was found to be an independent significant predictor for MI. Thompson et al. [21] showed that patients with stable angina were at greater risk of subsequent MI if CRP was elevated. Haverkate and colleagues [11] reported a positive correlation between elevated levels of CRP and history of MI, and confirmed the predictive value of CRP for coronary events in both stable and unstable angina. It has also been reported that high fibrinogen levels were associated with increased risk of future MI and history of MI [22,23]. However, we could not establish a significant relation between fibrinogen and history of MI. The ability of CRP to predict future events was demonstrated by Liuzzo et al. [24], who showed that CRP in

LAD = left anterior descending
CX = circumflex
RCA = right coronary artery

patients with unstable angina predicted recurrent ischemic events. Becker and co-workers [25] reported that elevation of fibrinogen at the time of hospital admission is associated with coronary ischemic events in patients with unstable angina. Our study population did not include patients with unstable ischemia, but in those who developed unstable ischemic chest pain, only baseline CRP levels were found to be higher, not fibrinogen nor AT-III.

One study found no correlation between the degree of atherosclerosis and the acute-phase response in patients with chronic stable angina, despite much more extensive atherosclerotic involvement [24]. On the other hand, another study demonstrated that CRP was positively correlated with the extent of coronary stenosis [11]. In our study, no relation was found between acute-phase response and extent of CAD, but in contrast to other studies we found significantly high levels of CRP in LAD disease among patients with single vessel disease.

In conclusion, the present research demonstrates the association of elevated CRP levels with CAD and extends this association to patients with history of MI, and also single vessel LAD disease. In addition, elevated CRP levels at the time of admission to hospital seem to be a predictor of in-hospital ischemic events in patients with stable angina. There is a significant relation between elevated levels of fibrinogen and CAD; however, our results are not clear regarding the association of AT-III levels with CAD.

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If a house be divided against itself, that house cannot stand

The Book of Mark 3:5