

C-Reactive **Protein** Blood Levels in Jordanians **With** Cardiac and Noncardiac **Chest Pain**

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Background: Inflammation plays a major role in the initiation and progression of coronary atherosclerosis. CRP, a key inflammatory marker, is elevated in patients with acute coronary syndrome (ACS) due to myocardial necrosis in acute myocardial infarction (AMI), and due to inflammation within the unstable plaque in unstable angina (UA). CRP levels have not been studied previously in Jordanians with chest pain of cardiac and noncardiac origin. Methods: We measured CRP blood level (mg/dl) in 358 consecutive patients evaluated for chest pain. Patients were diagnosed to have AMI, UA, or non-ACS (including chronic stable angina [CSA], or noncardiac chest pain [NCP]). Results: The mean age of the group was 51.9 years (range 28-80) and 84% were men. AMI was diagnosed in 143 patients (40%), UA in 57 (16%), and non-ACS in 158 (44%). Mean (\pm SD) CRP level in AMI was significantly higher than that in non-ACS (24.9 ± 39.9 vs. 1.44 ± 3.3 , $P=0.0001$), so was the mean CRP level in UA compared with that in non-ACS (14.8 ± 32.2 vs. 1.44 ± 3.3 , $P=0.006$). Although mean CRP in AMI was higher than in UA, the difference was not statistically significant ($P=0.16$). There was no difference between mean CRP levels in ST elevation MI and non-ST elevation MI (27.4 ± 43.2 vs. 20.6 ± 33.5 , $P=0.19$) or anterior vs. non-anterior MI (28.4 ± 38.7 vs. 26.4 ± 47.9 , $P=0.8$). Mean CRP among all patients with ACS ($n=200$) was significantly higher than CRP in CSA patients (22 ± 38 vs. 2.1 ± 5.2 , $P=0.05$) and higher than that in healthy individuals with NCP (22 ± 38 vs. 1.3 ± 2.9 , $P=0.0001$). CRP levels in CSA and healthy individuals with chest pain were not different ($P=0.88$). Conclusion: In this first large study of CRP levels in Jordanians with chest pain, high CRP levels were not only associated with AMI but also with UA, compared with CSA and healthy individuals with NCP, implicating the presence of inflammatory process within the unstable coronary plaque.



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Introduction

Experimental and clinical studies have demonstrated that inflammation plays a key role at all stages of atherosclerotic cardiovascular disease evolution including initiation, progression, and complications (1-3). Elevated blood levels of C-reactive protein (CRP), a key inflammatory marker, are associated with collagen vascular diseases, infections, and neoplasms. CRP levels rise following

acute myocardial infarction (AMI) due to myocardial necrosis. Patients with unstable angina (UA) with no evidence of MI, have higher-than-normal levels of CRP due to inflammation within the unstable coronary plaque (4). This study was conducted to evaluate CRP levels in patients presenting with acute chest pain of cardiac and noncardiac causes, and whether AMI and/or UA have higher CRP levels compared with those with no ACS.

Methods

Three hundred fifty eight consecutive patients who presented to the hospital for chest pain had their CRP blood levels measured on admission (mg/dl). The final diagnosis of the etiology of chest pain was based on clinical, electrocardiographic, echocardiographic, two 8-hour apart troponin T blood tests, stress testing, and/or coronary angiographic evaluation. AMI was ruled out by negative serial troponin T tests. Patients with obvious inflammatory or infectious dis-

ease were excluded. Each patient was fit into one of three groups. Group 1; patients with AMI; including ST elevation myocardial infarction (STEMI) and non-ST elevation MI (NSTEMI), group 2; UA, and group 3; non-acute coronary syndrome (non-ACS) patients including chronic stable angina (CSA) and non-cardiac chest pain (NCCP) in cardiac patients, and NCCP in healthy individuals.

Statistical methods: For each group, mean CRP levels were measured, as well as the percentage of patients within

three CRP strata (<0.3, 0.31-0.99, and >1.0). Tests of differences between groups were performed using chi-square test.

Results

Table 1 shows the clinical characteristics of the enrolled patients, as well as their distribution on the 3 clinical groups. Mean age of ACS patients was 55 years, 8 years older than non-ACS individuals. Diabetes and smoking were more prevalent among ACS than non-ACS individuals, but hypertension was more prevalent among UA than AMI and non-ACS. Mean CRP level in AMI patients was significantly higher than non-ACS (24.9+39.9 vs. 1.44+3.3, P=0.0001), so was the mean CRP level in UA compared with that in non-ACS (14.8+32.2 vs. 1.44+3.3, P=0.006). Although CRP was higher in AMI than UA, the difference was not statistically significant (P=0.16). Mean CRP in ACS patients (n=200) was significantly higher than CSA (22+38 vs. 2.1+5.2, P=0.05), and than NCP (P=0.88).

UA patients had CRP significantly higher than NCP in healthy individuals (14.6+32.2 vs. 1.3+2.9, P= 0.0034), table 2.

Mean CRP in patients with STEMI (27.4+43.2) was significantly higher than any of the subgroups of non-ACS patients: CSA (2.1+5.2, P=0.006), NCP in CAD patients (1.7+2.9, P=0.01), and NCP in healthy individuals (1.3+2.9, P=0.0001). UA patients had significantly higher mean CRP than healthy individuals with NCP (P=0.003). On the other hand, mean CRP among CSA patients was not different from healthy individuals with NCP (P=0.88).

Among AMI patients, mean CRP levels in STEMI (27.4+43.2) was not different from NSTEMI (20.6+33.5, P=0.19) or UA (14.8+32.2, P=0.76). Similarly, mean CRP levels in patients with acute anterior and non-anterior wall STEMI patients were not different (28.4+38.7 vs. 26.4+47.9, P=0.8).

When CRP levels in all patients were divided into three strata (<0.3, 0.31-

Patients	N (%)	Mean age (years)	Men (%)	Hypertension (%)	Diabetes (%)	Cigarette smokers (%)
All patients	358 (100%)	51.9	84%	24%	27%	42%
Group 1 AMI	143 (40%)	55.9*	83%	22%	36%++	55%**
Group 2 UA	57 (16%)	54.6*	84%	35%+	47%++	40%**
Group 3 Non- ACS	158 (44%)	47.3	84%	22%	11%	30%

ACS=acute coronary syndrome; AMI=acute myocardial infarction; UA=unstable angina.
 * P=0.0001 (older age for MI and UA) compared with non-ACS.
 + P=0.04 (more hypertension among UA than MI and non-ACS).
 ++ P=0.0001 (more diabetes among AMI and UA than non-ACS).
 ** P>0.002 (more smokers among AMI and UA than non-ACS).

Table 1 - Clinical characteristics of all participating patients and of the three clinical groups

Group	mean CRP (+SD)
Acute MI	24.9±39.9
Anterior wall MI	28.4±38.7
Non-anterior wall MI	26.4±47.9
Non-ST elevation MI	20.6±33.5
ST elevation MI	27.4±43.2
Nonsmokers with ST elevation MI	
- diabetics	51±61.7
- nondiabetics	52±63.9
Smokers with ST elevation MI	
- diabetics	19.7±22.4
- nondiabetics	11.7±12.5
Unstable angina	14.8±32.2
All ACS	22±38
Non-ACS	1.44±3.3
Chronic stable angina	2.1±5.2
Noncardiac pain in cardiac patients	1.7±2.9
Noncardiac pain in healthy persons	1.3±2.9

For (P) values, see text.Ω

Table 2 - Mean CRP levels (mg/dl) in the clinical groups and corresponding subgroups

0.99, and >1.0), the majority (88.5%) of ACS patients had CRP >1.0 compared with 26.6% of non-ACS patients ($P=0.0001$), and only 11.5% of the ACS patients had CRP levels of <0.3 compared with 72.8% of non-ACS patients ($P=0.0001$), table 3.

Mean CRP levels in patients with STEMI, were not different when calculated according to the presence or absence of diabetes and/or smoking. Although mean CRP levels among non-smokers, whether diabetics (51.0+61.7)

CRP level (mg/dl)	ACS N=200	Non-ACS N=158	P value
< 0.3	23 (11.5%)	115 (72.8%)	0.0001
0.31 - 0.99	0	1 (0.6%)	-
> 1.0	177 (88.5%)	42 (26.6%)	0.0001

Table 1 - Three CRP strata in patients with and without acute coronary syndrome (ACS)

The study showed that the mean age of AMI patients in Jordan is in the mid-fifties, similar to that in other local clinical and angiographic studies

or nondiabetics (52.0+63.9) were higher than levels among smoker diabetics (19.7+22.4) and smoker nondiabetics (11.7+12.5), the differences were not statistically significant. Similar conclusions were reached for all ACS patients as well.

When a CRP level of >5 was taken as a cut off point, the sensitivity and specificity for the presence of ACS were 73% and 90%, respectively, with a positive and negative predictive values (PPV and NPV) of 90% and 72%, respectively. When the cut off level is lowered to 0.0, the corresponding values are 89% (sensitivity), 73% (specificity), 81% (PPV), and 83% (NPV).

Discussion

CRP, a 1.15 kD peptide composed of five identical subunits, is synthesized by hepatocytes in response to interleukin-6 released from monocytes during the inflammatory process (5). Atherosclerosis involves inflammatory response at all of its evolution phases, from fatty streaks

to plaque rupture (6-8), and hence, higher-than-normal levels of CRP increase in the circulation in the absence of myocardial necrosis. Prospective studies have shown that CRP is a predictor of coronary heart disease in apparently healthy men and women, with a stepwise progression in risk of MI and stroke with increasing CRP levels over 8 years of follow up (9-12).

In patients with coronary disease, CRP predicts adverse clinical cardiac and cerebral events (13-15). Clinical studies showed that in UA patients with no myocardial necrosis and negative serial troponin measurements, elevated CRP is indicative of plaque inflammation (16,17). In our study, this was supported by higher mean CRP level in UA patients compared with non-ACS patients, with no statistically significant difference from the mean CRP in AMI patients. Moreover, significantly higher percentage of ACS patients had high CRP (>1.0) compared with non-ACS patients. UA patients also had higher mean CRP level than healthy individuals with noncardiac chest pain.

AMI patients had similar CRP levels irrespective of the type (ST-elevation vs. non-ST elevation), and location (anterior vs. non-anterior) of the infarction. Furthermore, the presence or absence of diabetes and/or smoking did not significantly influence the CRP levels among AMI or ACS patients despite a trend of higher CRP in non-smokers, compared with smokers, regardless of the presence or absence of diabetes.

CRP levels vary according to genetic and environmental factors; hence CRP levels vary in ACS patients in different geo-

graphic regions. In a study from Egypt (18), mean CRP in AMI was significantly higher than UA (41 vs. 9.2 mg/dl), and in anterior MI, CRP was higher than in inferior MI (51 vs. 18 mg/dl, respectively).

Although sensitivity and specificity values of CRP cut-off levels of 0 or 5 mg/dl were relatively high for their diagnostic yield of ACS in our study, the main pillars for diagnosing ACS will remain the standard clinical, electrocardiographic, and enzymatic criteria.

The study showed that the mean age of AMI patients in Jordan is in the mid-fifties, similar to that in other local clinical and angiographic studies (19,20). This is about 10 years younger than the mean age of AMI patients in the west.

A study is currently underway (CRP and PRognosis In acute coronary Syndrome, CAPRIS) to evaluate the prognostic impact of CRP on future cardiac events in ACS patients in Jordan.

No clear recommendation has been published, so far, advocating measuring CRP as a screening for the whole population. Individuals with high CRP can benefit from aggressive risk factor modification; as well medications that have

been found to lower the CRP blood level such as aspirin, angiotensin II receptor blockers, and statins (21, 22). The latter can lower CRP level independent of their low-density lipoprotein cholesterol lowering effect.

Limitations of the study: Although we did not use the high-sensitive CRP assay, ACS patients have CRP levels that can be detectable by routine assays. Such assays have used in several ACS clinical studies. High-sensitive (hs) and ultrasensitive (us) CRP assays are mainly used in apparently healthy individuals for prediction of future cardiovascular events and development of hypertension. We did not study the impact of CRP level on

prognosis in ACS (23,24). A study is currently underway (CRP and Prognosis In acute coronary Syndrome, CAPRIS) to evaluate the prognostic impact of CRP on future cardiac events in ACS patients in Jordan.

Conclusions: In this first study of CRP in Jordanians with acute coronary syndrome, we found that serum CRP is elevated not only in patients with AMI, but also in those with UA, implicating presence of inflammation within the unstable coronary plaque. Mean CRP level in ACS patients is significantly higher than that in patients with stable CAD or noncardiac chest pain. Prognos-

tic implications of CRP await an ongoing study.

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