C-Reactive Protein and Vascular Disease

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C-reactive protein has long been known as a non-specific inflammatory marker. Considered to be an acute-phase reactant to infective and non-infective inflammation, CRP constitutes an optimal marker for their identification and evaluation [1]. In addition, recent studies have suggested that CRP might be considered as a risk factor for vascular diseases. It binds to low density lipoprotein cholesterol, and, by stimulating the monocytes to induce increased production of tissue factor and subsequent thrombosis, activates the complement pathway and neutralizes the platelet-activating factor [2,3].

In the last decade several articles were published on the relationship between CRP and coronary artery disease. Juhan et al. [4] and Liuzzo et al. [5] elucidated the high correlation between unstable coronary disease, its recurrence, the need for repeated interventional treatment, the prognosis, and the serum levels of CRP. Other investigators showed a very significant positive correlation between CRP levels and the incidence of acute coronary events, and between CRP levels and the extent of the arteriosclerotic disease [6–8].

The above mentioned studies were used as the cornerstones for others, which had also confirmed the same significant correlation [4–8]. The Multiple Risk Factor Interventional Trial (MRFIT) [9] conducted a 17 year follow-up study of 12,866 asymptomatic males aged 35–37 years who were known to have high risk for coronary heart disease. The serum of each male was taken and frozen upon entering the study. A direct correlation between the level of CRP upon entering the study and coronary death was confirmed.

Based on these studies, it was suggested that high levels of CRP in patients with ischemic heart disease directly correlated with a poor prognosis. Other investigations, such as ECAT (European Concerted Action on Thrombosis and Disabilities) [10], demonstrated that the CRP levels at entry to the study were significantly higher in patients who had survived an acute coronary event. The Physician's Health Study [11] revealed two additional conclusions: the first, that treatment with aspirin as a primary prevention for coronary events was more effective in patients with high CRP levels; and the second, that detecting CRP level could be a relevant marker for predicting future occurrences of myocardial infarction. Other trials, including the Cardiovascular Health Study [12] and the FRISK Study [13], reinforced the above mentioned positive correlation between the high levels of CRP and the occurrence of coronary events or coronary death.

The strong link between high levels of CRP and coronary events and deaths is undergoing further research because of the attractive theory that inflammation is considered to be the basis of atherosclerosis. The TIMI 11A Study [14], for example, which measured CRP levels for 2 weeks in patients with unstable angina and non-Q wave myocardial infarction, found that CRP levels were significantly higher in patients who died because of coronary event than in patients who survived (7.2 mg/L and 1.3 mg/L, respectively). The study also found that the high rate of mortality occurred in patients who, in addition to having high CRP levels, also had high troponin T. The study concluded that in patients with unstable angina or non-Q wave myocardial infarction, high CRP levels and not troponin T levels mark them to be at high risk of mortality. The authors of another major study, the CARE study (Cholesterol and Recurrent Event) [15], came to a similar conclusion. They found that in patients with significantly higher levels of CRP the relative risk of occurrence of acute coronary events and/or coronary deaths was 75% higher than in patients who had a lower level of CRP. Rebuzzi et al. [16], in evaluating the CRP and troponin T levels in about 100 patients with unstable angina, found that CRP level had the higher sensitivity (87%) for identifying future candidates for myocardial infarction. In addition, the prognostic value of CRP and troponin T levels together was higher than the value of the electrocardiogram and symptomatology.

In the Women's Health Study [17], a primary prevention study of 39,876 menopausal healthy women, vascular events occurred in 122 women in whom the CRP levels were significantly high, while no event occurred in women with normal levels of CRP. The risk of vascular event among the women with high levels of CRP was significantly higher than among those with normal CRP levels ($P = 0.0001$). Women with significantly higher levels of CRP were at 5 times the estimated risk for the incidence of any vascular event, and at 7 times the estimated risk for an acute coronary event ($P = 0.0001$). They concluded that by evaluating CRP levels in healthy women, it might be possible to predict a future occurrence of vascular events.

CRP = C-reactive protein

Gaspardone and colleagues [18] observed that all the coronary events following stent implantation occurred in patients whose CRP levels were high during the implantation. Anderson et al. [19], when evaluating 363 catheterized patients, also found a significant association between high levels of CRP and coronary disease. Today it is widely agreed that the CRP level serves as a predictive prognostic marker in patients who survived a myocardial infarction. Anzai and co-workers [20] noted a high correlation between myocardial rupture and high levels of CRP in patients who had suffered an acute myocardial infarction. In addition, Pietila et al. [21] and Andreotti et al. [22] found that a low level of CRP in patients treated with thrombolytic therapy is a marker for better coronary reperfusion and smaller area of myocardial necrosis.

On the other hand, it is important to state that not all researchers agree with this conclusion. Oltrona's group [23] found high CRP levels in 140 unstable angina disease patients but without prognostic significance for future occurrence of coronary events. Similar results were found by Benamer and colleagues [24] in their study of 195 unstable angina disease patients. Finally, Curzen et al. [25], investigating 72 patients who complained of angina pectoris, did not consider CRP as a prognostic marker for future occurrence of coronary events.

In addition to the direct correlation between CRP level and cardiovascular disease, CRP's close association with stroke – as a risk factor and/or as a marker or as a prognostic marker – was also evaluated. Earl and Wayne [26] showed that after adjusting for age, gender, race or ethnicity, education, smoking status, systolic blood pressure, serum cholesterol, high density lipoprotein cholesterol, history of diabetes mellitus, body mass index, and physical activity, the odds ratio for stroke among patients with CRP concentrations $\geqslant 0.55$ mg/dl compared to patients with concentrations $\leqslant 0.21$ mg/dl was very significant. These cross-sectional data support findings from other studies suggesting that CRP concentration may be a risk factor or marker for stroke. Jacobijn et al. [27] also noted that CRP is a strong but non-specific risk factor of fatal stroke in old persons, but this finding does not support the idea that CRP has direct vascular effects that underlie fatal cerebrovascular disease.

The association between CRP level and peripheral vascular disease was also evaluated. Ridker's team [28] examined a database of patients who were included in the Physician's Health Study [11] and found a positive correlation between CRP levels and both the occurrence and risk of peripheral vascular disease. They also showed that patients with higher levels of CRP required more invasive treatment.

In a recent meta-analysis of prospective studies [29] evaluating the relation of CRP levels and vascular disease, it was suggested that the CRP level could be added to the other known atherosclerotic risk factors for prediction of coronary, cerebral and peripheral vascular diseases.

Despite the varied observations mentioned above, the mechanisms that could explain the direct correlation between the level of CRP and the prognosis of cardiovascular disease are not yet fully clear. Actually, the most accepted theory is that chronic inflammation – usually presented in the diseased coronary arteries, which could be related to an infectious etiology or to other chronic inflammatory diseases [7,30–36] – is responsible for the phenomenon. Torzewski et al. [37] have shown that the atheromatotic plaques are usually enriched with CRP, which is a possible factor in the atherosclerotic process as it activates the complement system and proliferation of the foam cells. Others believe that CRP may be a preliminary marker for high blood concentration of coagulation factors, which are usually considered to be part of the pathophysiology of the atherosclerotic process [38]. On the other hand, Liuzzo et al. [39], and Biasucci et al. [40] have shown that myocardial ischemia and activation of the coagulation system, respectively, did not provoke high CRP concentration. Other researchers [41] demonstrated that a high concentration level of CRP co-localizes with activated complement components in the necrotic zone of myocardial infarction. As an additional explanation they stated that CRP may directly interact with the atherosclerotic vessels or the ischemic myocardium by activation of the complement system, thereby promoting inflammation and thrombosis. Current studies [42] investigating the effect of thrombolytic agents in acute myocardial infarction are oriented to the possible correlation between resistance to thrombolysis and CRP concentration. They hypothesize that intense inflammatory reaction might be an expression of a more organized and resistant thrombus.

Conclusion

In recent years there is increasing evidence that atherosclerosis is a chronic inflammatory disorder resulting from a combination of processes, and that acute exacerbation of this inflammation is associated with acute coronary syndromes, carotid arteries and peripheral vascular disease exacerbation. It is likely that some inflammatory markers will actually be considered as cardiovascular risk factors. In this respect, the acute-phase reactant CRP is of special interest. It has been shown that baseline levels of CRP in apparently healthy persons, in patients with stable angina pectoris, in patients with carotid artery disease, and in patients with peripheral vascular disease, can be considered as an independent risk factor for cardiovascular events, strokes, and peripheral vascular disease aggravation respectively; whereas the rise in CRP after myocardial infarction, during unstable angina pectoris or peripheral vascular disease aggravation, could also predict and correlate with the prognosis and outcome of these patients. We believe that this simple and economic diagnostic tool should be considered as one of the elements that constitute the cornerstone for classification and risk stratification of patients with suspected myocardial, cervical, vascular and peripheral vascular injury. We can anticipate that future studies will reveal whether CRP level has an important role in assessing and treating these patients.

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