An elevated level of C-reactive protein (CRP), an acute phase protein, is one of many downstream indicators of inflammation. Physiologically, CRP enhances cell-mediated immunity by promoting phagocytosis, accelerating chemotaxis, and activating platelets. The purposes of this article are (1) to review the clinical data implicating serum CRP level as a systemic marker of focal inflammation and (2) to explore serum CRP level as a reflection of the inflammatory component of atherogenesis. Our findings indicate that CRP levels serve as an early marker of the magnitude of inflammation in events as dissimilar as appendicitis and myocardial infarction. The level of circulating CRP correlates with endovascular disease and may serve to identify otherwise asymptomatic patients at sufficient cardiovascular risk to warrant aggressive therapy. Determining whether CRP has a direct pathologic role in the vascular wall itself may have the most clinical relevance.

Arch Surg. 2003;138:220-224

Systemic inflammation is associated with leukocyte-mediated endothelial dysfunction. Proinflammatory cytokines, chemokines, and glucocorticoid hormones are elaborated and stimulate hepatocytes to synthesize a wide array of acute phase proteins (Figure). A dominant acute phase protein in mammals, C-reactive protein (CRP) is a 206–amino acid pentameric polypeptide. Originally isolated from the serum of patients with pneumonia, it has a high binding affinity for pneumococcal C polysaccharide. Although CRP level correlated with infection, this qualitative relationship did not predict disease severity. By the 1980s a sensitive and specific quantitative assay for CRP was commercially available. Subsequently, mounting clinical evidence suggests an early quantitative correlation between plasma CRP levels and several inflammatory states.

Rapidly synthesized acute phase proteins support host defenses by neutralizing offending antigens, controlling tissue damage, and promoting tissue repair. C-reactive protein acts as an opsonin for invading bacteria and circulating immune complexes. C-reactive protein may also activate the complement cascade and scavenge chromatin after cellular necrosis. These functions promote phagocytosis, accelerate chemotaxis, and activate circulating platelets. Ultimately, CRP accelerates the clearance of microbial debris from the circulation and enhances cell-mediated immunity. Plasma levels of CRP can be detected as early as 4 hours after injury and peak (1000-fold increase) between 24 and 72 hours after injury. The purposes of this article are (1) to review the clinical data implicating CRP level as a systemic marker of focal inflammation, (2) to explore CRP level as an indicator of the endovascular inflammation that leads to atherogenesis, and (3) to examine anti-inflammatory strategies against atherosclerosis.

C-REACTIVE PROTEIN AND SURGICAL DISEASE

C-reactive protein is a reliable early indicator of inflammation or injury. Mustard and colleagues documented that serial postoperative CRP levels could predict septic complications before their clinical manifestation. Indeed, serial CRP levels in
trauma patients aid in the discrimination of bacterial sepsis from noninfectious systemic inflammatory response syndrome. A cutoff value of 17 mg/dL or more for CRP gives a sensitivity of 74% and a specificity of 75% in predicting the presence of infection. Level of CRP also predicts the severity of acute cholecystitis (>10 mg/dL is strongly related to tissue necrosis) and serves as an accurate marker in risk assessment for postoperative amputation in patients undergoing femoropopliteal bypass.

If CRP level indicates local infection, can CRP levels enhance the precision of the difficult diagnosis of common entities such as acute appendicitis? A large retrospective study has documented that the sensitivity of CRP in these patients is greater than 90%. Furthermore, the negative appendectomy rate is reduced by approximately 8% if surgery is canceled in patients with CRP levels and white blood cell counts within the reference range. Eriksson and colleagues prospectively measured serial CRP and white blood cell levels in patients with suspected appendicitis. Levels were determined every 4 hours following admission and the operating surgeon was blinded to all but initial values. The sensitivity of CRP level in predicting appendicitis was 60% on admission and increased to 100% by the fourth draw. Conversely, white blood cell counts exhibited a sensitivity of 95% on admission, but dropped to 75% by the fourth draw. Multiple studies confirm that an elevated CRP level serves as a systemic marker of focal inflammation and infection.

INFLAMMATION AND CARDIOVASCULAR DISEASE

Accumulating data pathologically link atherosclerosis and the inflammatory response to vascular injury. Luminal injury associated with hyperlipidemia, hypertension, and/or angioplasty results in endothelial cell dysfunction, adhesion molecule expression, and inflammatory cell infiltration. The autocrine and paracrine effects of cytokines and chemokines promote oxidized lipid deposition with vascular smooth muscle cell proliferation and migration. This chronic vascular wall inflammation leads not only to progressive luminal stenosis but also to plaque instability. Thus, a systemic marker that identifies the patient with “smoldering” vascular inflammation is intuitively attractive.

Several prospective studies have demonstrated a direct correlation between acute myocardial infarction (MI) rise in CRP, postinfarction adverse events, and subsequent infarct size (Table). The European Concerted Action on Thrombosis and Disabilities (ECAT) Angina Pectoris Study also reported elevated CRP levels in more than 2000 outpatients with stable and unstable angina. This study identified a 2-fold increase in the risk

<table>
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<th>Source</th>
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<td>CRP an independent predictor of PAD</td>
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Abbreviations: CRP, C-reactive protein level; CVD, cardiovascular disease; MI, myocardial infarction; PAD, peripheral arterial disease.

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of MI and sudden cardiac death in any patient with a CRP level greater than 0.36 mg/dL. Toss and colleagues observed more than 900 patients with unstable angina or non–Q-wave infarction and reported a positive correlation between elevated CRP level and mortality. Thus, an elevated CRP level does appear to correlate with incidence of acute coronary syndromes.

Elevated CRP Level as an Indicator of Endovascular Instability

Elevated CRP level is also associated with an increased risk of both 30-day mortality and MI following angioplasty. Elevated preangioplasty CRP levels of greater than 0.3 mg/dL predicted an increased rate of procedural and in-hospital complications. At 1-year follow-up, clinical restenosis developed in 63% of patients with high preangioplasty CRP levels vs only 27% of those with values in the reference range. Milazzo and colleagues reported a similar trend in 86 patients who underwent elective coronary artery bypass grafting. Twenty-five percent of patients with initial CRP values of 0.3 mg/dL or higher experienced postoperative ischemic events, vs only 4% of those with values in the reference range.

Direct CRP-Mediated Vascular Disease

The evolving concept of CRP acting as a direct pathologic mediator in vascular remodeling may ultimately provide the most clinical relevance. C-reactive protein has been localized to the neointima of atherosclerotic plaque and activates complement in early lesions. Although hepatic production has classically been identified as the primary source, Yasojima and colleagues demonstrated that CRP is also expressed by vascular smooth muscle cells and macrophages resident in atherosclerotic lesions. Furthermore, CRP induces endothelial cell expression of adhesion molecules and monocyte chemotactic protein. Recently, Fu and Borenstajn demonstrated that CRP promotes the aggregation of low-density lipoprotein, thus contributing to foam-cell formation within atherosclerotic lesions. This local influence, coupled with the well-documented proinflammatory effects of CRP on monocytes and macrophages, supports a direct deleterious role of CRP in the vascular wall itself.

Elevated CRP Level in Asymptomatic Patients

Several small cross-sectional and case-control studies have even suggested that CRP levels may be predictive of cardiovascular disease in asymptomatic patients. The Multiple Risk Factor Intervention Trial (MRFIT) was the first prospective study to report the relationship between CRP and coronary disease in asymptomatic, but high-risk, men. In this 17-year study, increased CRP levels directly correlated with mortality. Results from the Physicians’ Health Study, a randomized, double-blind trial of treatment with aspirin and beta carotene in the prevention of cardiovascular disease, also documented the link between CRP levels and risk of MI and stroke in healthy men. Interestingly, when smoldering endovascular inflammation is suppressed with aspirin therapy, risk reduction is directly related to CRP levels. The Monitoring Trends and Determinants in Cardiovascular Disease (MONICA) study measured CRP levels in healthy men with an 8-year follow-up. This study also identified an association between elevated CRP levels and the risk of both fatal and nonfatal MI in 936 patients. Recently, the Speedwell Prospective Study also correlated systemic inflammation and ischemic heart disease and reported a decrease in CRP level with smoking cessation in more than 1000 men. High CRP levels have also proven to be predictive of adverse cardiovascular events in healthy women and the elderly. Not surprisingly, a positive association has been found between CRP level and the risk of developing peripheral arterial disease.

ANTI-INFLAMMATORY THERAPY

Antiplatelet and/or lipid-lowering agents have traditionally been used for the prevention of acute cardiovascular events. An evolving pharmacologic paradigm links these drugs and serum CRP levels. The Nurses’ Health Study analyzed the incidence of coronary events in more than 80,000 women who were taking aspirin regularly. Overall, 1 to 6 aspirin tablets per week resulted in a decrease in nonfatal MI and fatal coronary disease. These results have been corroborated in several large, randomized studies. Ridker and colleagues documented that the benefit of aspirin therapy was greatest in healthy men with the highest CRP levels. Although the risk reduction of MI in this group was 55.7%, the beneficial effect was reduced as CRP levels decreased. These data emphasize the inflammatory component of cardiovascular disease and suggest that aspirin therapy may directly affect endovascular dysfunction, as indicated by CRP production. Furthermore, CRP level may serve as an indicator of patients at risk and as a practical marker of the efficacy of the preventive strategy.

Several large trials have linked the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) to the attenuation of serum CRP levels. Recently, the Air Force/Texas Coronary Artery Prevention Study investigators reported the effects of lovastatin on CRP levels in patients with and without hyperlipidemia. Apart from its lipid-lowering effects, lovastatin reduced CRP levels by 14.8%. Lovastatin was effective in preventing coronary events in patients with elevated cholesterol levels and was also effective in patients with low cholesterol and high CRP levels. Thus, not only does CRP level reliably reflect inflammation, but its suppression is associated with a reduction in adverse cardiovascular events.

Although the effects of these prophylactic agents on CRP level are promising, there are concerns regarding widespread use of aspirin for primary prevention. A recent review of the cumulative experience with aspirin summarizes the results of 5 randomized studies. With the exception of one British study, 4 trials docu-
mented a reduction in the rate of MI in patients treated with aspirin. However, a meta-analysis evaluating these trials reported a 69% increase in bleeding complications. Thus, aspirin prophylaxis can be justified only in patients who are at increased risk for cardiovascular events. Sanmuganathan and colleagues recommend preventative aspirin therapy only in patients with a coronary event risk of at least 1.5% per year.

In addition to nausea, abdominal discomfort, and headaches, all statins pose the risk of myopathy and fatal rhabdomyolysis. The mechanism of skeletal muscle toxic effects is likely due to inhibition of drug metabolism and subsequent increase in plasma statin concentrations. In addition, statins interact with a wide array of drugs, including immunosuppressants, azole antifungals, coumarin anticoagulants, and calcium channel antagonists. Despite their widespread use in cardiovascular patients, the precise mechanism by which aspirin and statins reduce CRP levels is unknown. Although the anti-inflammatory effects of each agent are well documented, it is unknown whether these drugs mediate CRP expression directly or whether this effect is secondary to a decrease in well-described inflammatory promoters of CRP production.

While the prognostic role of CRP levels in numerous surgical diseases is still being defined, its value in risk stratification of cardiovascular patients is increasingly convincing. Recently, Ridker and colleagues reported that serum CRP levels might be more predictive than low-density lipoprotein cholesterol levels of adverse cardiovascular events. More than 75% of patients with elevated CRP levels experienced a major cardiac event despite low-density lipoprotein cholesterol levels that were lower than the threshold recommended for pharmacologic intervention. The implications of these observations are significant in that patients not receiving statins and other risk-factor modifications may, in fact, require aggressive therapy.

This study was supported by grants GM49222 and GM08315 from the National Institutes of Health, Bethesda, Md (Dr Harken).

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REFERENCES