Coming of Age of C-Reactive Protein
Using Inflammation Markers in Cardiology
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In a recently published prospective study comprising 28,000 women, Ridker et al showed that C-reactive protein (CRP) is a better predictor of the risk of cardiovascular events than low-density lipoprotein (LDL) cholesterol. The implication of this and many other supporting studies is profound and will change the way we screen and manage our patients with atherosclerosis and its associated clinical syndromes. CRP is one of the acute phase proteins that increase during systemic inflammation. Individuals without inflammation usually have CRP levels below 1 μg/mL; however, patients with bacterial infections, autoimmune diseases, and cancer frequently have CRP level as high as 100 μg/mL or even higher. It is clear that a high CRP level has no specificity in differentiating disease entities from one another. Despite its lack of specificity, CRP has now emerged as one of the most powerful predictors of cardiovascular risk. Even more remarkable, CRP’s predictive power resides in the range between 1 to 5 μg/mL, which was previously regarded to be normal in the era preceding the high-sensitivity CRP test. In fact, tests showing serum CRP levels greater than 10 μg/mL in apparently healthy men or women should be repeated to exclude occult infection or other systemic inflammatory process (see Figure). To understand CRP’s transition from an acute phase protein to a most useful inflammatory biomarker for predicting future cardiovascular events, we must know more about the role of the immune system in the pathogenesis of atherosclerosis.

CRP as a Biomarker of Inflammation
Atherosclerosis is now widely accepted as a chronic inflammatory disorder that is initiated by vascular injury induced by oxidized LDL, reactive oxygen species, diabetes, infection, etc. When comparing atherosclerosis to rheumatoid arthritis, a bona fide autoimmune disease, a remarkable pattern of similarity emerges, in that both have evidence for activation of macrophages, B cells, T cells, and endothelial cells, alteration in the Th1/Th2 ratio, and elevation of inflammatory cytokines. A key feature in the inflammation hypothesis is the recognition that circulating immune cells are recruited to the inflamed vessel by interacting with adhesion molecules and chemokines. Presently, it is not possible to determine directly the level of adhesion molecules expression on endothelial cells in patients. However, one can assay for the circulating level of adhesion molecules, inflammatory cytokines, or acute phase proteins relatively easily. In a direct comparison of a panel of inflammatory and lipid markers in predicting cardiovascular events, CRP surpasses all other biomarkers, including LDL cholesterol. CRP’s strong predictive value may be explained by its long-term stability during storage, its long half-life, its lack of diurnal variation, and its lack of age and sex dependence. It is also likely that CRP’s proatherogenic property contributes to the robustness of its predictive power.

CRP derives its name as a protein that binds to the C-polysaccharide of the pneumococcal cell wall. It is part of the innate immunity that activates the classical complement pathway after aggregation or binding to ligands. CRP also binds to phospholipids of damaged cells, with subsequent limited activation of the complement system and enhanced uptake of these cells by macrophages. Recently, CRP was shown to possess proatherogenic properties. For example,
CRP activates endothelial cells to express adhesion molecules, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, selectins, and the chemokine, monocyte chemotactic protein-1. CRP also induces the secretion of interleukin-6 and endothelin-1 and decreases the expression and bioavailability of endothelial nitric oxide synthase in human endothelial cells. Furthermore, CRP activates macrophages to express cytokine and tissue factor and enhances the uptake of LDL. We and others have found that CRP also amplifies the proinflammatory effects of several other mediators, including endotoxin. The concentration of CRP that elicits these proinflammatory responses in vitro experiments is in excess of 5 μg/mL. This concentration is higher than the serum concentration of 1 to 3 μg/mL that is associated with cardiovascular risk. Perhaps circulating CRP levels do not truly reflect tissue concentrations because CRP has been shown to be deposited in human atherosclerotic plaques, especially complex ones, and the locally concentrated CRP may be present in a sufficient amount to promote development of atherosclerosis.

**CRP as a Clinical Test in Cardiovascular Practices**

High-sensitivity CRP is widely available in most clinical settings throughout the world. When should we order the CRP test? How do we manage patients with high CRP levels? Results from the Women’s Health Study suggest that CRP determinations will be of value in primary prevention. We believe that CRP testing should be ordered along with lipid profiles to identify apparently healthy men and women at risk of developing cardiovascular events. The interpretation of CRP levels on the basis current data is summarized in the accompanying figure. Patients with CRP levels between 1 and 3 μg/mL are at intermediate risk and those with levels above 3 μg/mL at high risk. However, tests that show CRP levels above 10 μg/mL should be repeated to exclude other processes. CRP levels should be interpreted in conjunction with the lipid profile. It is particularly useful in patients with LDL cholesterol levels below 160 mg/dL, because 77% of all cardiovascular events occur among women with LDL cholesterol levels below this value. A more difficult question to answer is how to manage patients with LDL-cholesterol levels below 160 mg/dL and CRP levels greater than 1 μg/mL. We believe that these patients should receive low-cholesterol and low-fat diets and/or be placed on aggressive statin therapy to lower LDL cholesterol values to well below 100 mg/dL. Statins have been shown to reduce CRP levels by 25% to 50% in previous studies. Thus, this approach has the potential to lower the LDL cholesterol and CRP level simultaneously. A prospective, long-term study has been planned to test this hypothesis. Furthermore, CRP levels could be used to motivate patients to modify their lifestyles more aggressively. Recent studies have shown that losing weight and controlling diabetes also lower CRP levels. Thus, patients can use their CRP levels as an inflammation fitness score to monitor improvement in their cardiovascular health.

CRP levels predict clinical outcomes in acute coronary syndromes and may be used in conjunction with troponin I or T levels to identify high-risk patients for more aggressive management with antiplatelet agents and statins. Similarly, in patients undergoing percutaneous coronary interventions, CRP levels may alert the interventional cardiologist for closer monitoring of the patients or more aggressive management. Also, as we stated earlier, “the higher event rates noted in the cohorts with elevated serum CRP values suggest an excellent opportunity to screen and identify patients likely to benefit from novel anti-inflammatory strategies as adjunctive therapies to [percutaneous coronary intervention].”

Finally, CRP levels can also be used as a guide to start patients on acetylsalicylic acid (ASA) for primary prevention. As shown in the Physician Health Study, ASA usage of 325 mg every other day is most useful in males with CRP levels greater than 0.55 μg/mL. One wonders whether other antiplatelet therapies such as Plavix (Bristol-Myers Squibb) might be additive to ASA in reducing platelet–white blood cell interaction and inflammation, further lowering serum CRP values. This needs to be determined by future studies.

**Summary**

CRP is not only an excellent biomarker of inflammation, but it is also a direct participant in atherogenesis. It provides a valuable tool for identifying patients at risk of cardiovascular events in primary prevention in conjunction with lowering LDL cholesterol and may also have utility in the treatment of acute coronary syndromes and with percutaneous coronary intervention therapy. Finally, CRP will provide a readily accessible marker for further testing of the inflammatory hypothesis in atherosclerosis.

**References**

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