C-Reactive Protein and Cardiovascular Risk in the Metabolic Syndrome and Type 2 Diabetes: Controversy and Challenge

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C-reactive protein (CRP) has become the subject of avid interest in recent years, but the history of CRP began > 7 decades ago and has been one of discovery and continuing dispute. In 1930, Tillet and Francis observed a substance in the serum of people with pneumococcal infections that formed a precipitate when mixed with the C-polysaccharide coat of Streptococcus pneumoniae. This “C-reactive” activity was absent from the sera of healthy individuals. MacLeod and Avery subsequently found this substance to be a protein and coined the term “acute phase” to characterize the serum of patients with various acute infections. Lofstrom found a similar acute-phase response in acute and chronic inflammatory conditions, and CRP became recognized as a nonspecific acute-phase protein. Highly conserved in evolution, CRP has similar structural and functional homology in many species, even including the hemolymph of the horseshoe crab.

The story of CRP has evolved rapidly in the past decade. The development of high-sensitivity CRP (hs-CRP), a stable and inexpensive assay, has increased the potential to obtain more reliable determinations of circulating levels of this inflammatory cytokine, and thereby to refine cardiovascular risk assessment, particularly for those whose risk is intermediate, such as individuals with average levels of LDL cholesterol.

What Is C-Reactive Protein?
CRP is considered to be a major inflammatory cytokine that functions as a non-specific defense mechanism in response to tissue injury or infection. Synthesized mainly in the liver, CRP activity is stimulated by other cytokines, especially interleukin (IL)-6, IL-1β, and tumor necrosis factor-α (TNF-α). CRP binds to a variety of molecules, particularly liposomes and lipoproteins, such as LDL and VLDL cholesterol, and is a powerful activator of the classic complement system. Accumulating evidence suggests that CRP, which is also found within macrophages of atheromatous plaques, is causally or mechanistically related to atherothrombosis.

CRP and the Atherogenic Process
Whether CRP can mediate as well as predict the progression of atherosclerosis is under active investigation and is likely in some clinical conditions. A wealth of data suggests that chronic inflammation is a major factor that drives the progression of atherosclerosis and atherothrombosis. Diverse cardiovascular risk factors, such as smoking, high blood pressure, dyslipidemia, and hyperglycemia, play a proinflammatory role in the initiation of endothelial dysfunction and atherosclerotic plaque formation. The accumulation of lipids in the arterial wall is the result of a complex response that involves inflammation, and this inflammatory response promotes additional lipid accumulations (Figure 1). Elevated CRP levels are associated with diminished expression of endothelial nitric oxide (NO) synthase, which may attenuate production of NO, promote oxidative modification of LDL, and induce expression of plasminogen activator inhibitor-1.

CRP Can Predict Cardiovascular Events
Modest elevations of CRP can be found even in apparently healthy people. A progressive rise in CRP can reflect augmented stages of vascular inflammation, but the specific clinical conditions under which this occurs are incompletely understood. Although LDL cholesterol remains a major risk component for cardiovascular disease, at least one-third of coronary events occur in individuals with LDL levels < 130 mg/dl, which is generally considered an average level in individuals without overt coronary artery disease. Evaluation of CRP levels under those clinical conditions may be very
helpful in risk stratification. Reports that CRP levels are elevated during acute cardiovascular and cerebrovascular events suggest that CRP has value in predicting the subsequent occurrence of such events.\textsuperscript{13,14}

Results of the Scandinavian Simvastatin Survival Study suggested a potential increase in cardiovascular mortality in patients in the highest quartile of circulating CRP levels, particularly when these are evaluated with concomitant plasma lipoprotein levels.\textsuperscript{15} However, interpretation of these data is clouded by the presence of confounding variables.

Occurrence of first cardiovascular events in the observational Women’s Health Study appeared to rise incrementally with increasing baseline levels of CRP. Elevated levels of LDL cholesterol and CRP were individually associated with increased cardiovascular risk. However, combined elevations of both analytes improved risk prediction to a greater degree than either one considered individually.\textsuperscript{15}

A prospective observational study of \textgreater{} 15,000 middle-aged women apparently healthy at baseline was designed to determine the relative utility of standard lipoprotein, lipid, apolipoprotein, and CRP measures as predictors of 10-year cardiovascular event rates. The results provided some support for the additive prognostic value of CRP measurements.\textsuperscript{16} Nevertheless, more convincing data are required from randomized, prospective clinical trials to delineate the particular clinical conditions in which CRP measurements are useful.

**Cardiovascular Disease, Metabolic Disease, and Inflammation**

The metabolic syndrome has been defined as a cluster of risk factors for atherosclerotic cardiovascular disease that includes insulin resistance, dyslipidemia, abdominal adiposity, and often hypertension. Investigators have long hypothesized links between the metabolic derangements of insulin resistance syndrome/type 2 diabetes and the development and progression of atherosclerosis.\textsuperscript{17} A number of investigators have similarly concluded that IL-6 and CRP are associated with hyperglycemia, insulin resistance, and overt type 2 diabetes, and both are strong predictors of cardiovascular disease in apparently healthy people.\textsuperscript{18,20}

In a 10-year observational study\textsuperscript{21} of Dutch adults without diabetes or coronary heart disease (CHD) at baseline, the presence of the metabolic syndrome imparted a twofold increased risk for cardiovascular events. Similar results were found in an Italian survey study in which one-third of the study subjects were identified as having the metabolic syndrome at baseline.\textsuperscript{22} At the end of 5 years of follow-up, study subjects having the metabolic syndrome at baseline incurred a 3.7-fold increase in fatal and nonfatal CHD events compared with subjects without the syndrome at the start of the study.

**CRP and the metabolic syndrome**

The data showing the importance of CRP as an indicator of vascular inflammation and a predictor of future events in patients with the metabolic syndrome may be the most compelling. Among 8,570 participants in the National Health and Nutrition Examination Survey, the age-adjusted prevalence of elevated CRP was 29\% in people with the metabolic syndrome, compared with 12.1\% in those without the metabolic syndrome.\textsuperscript{23} In nondiabetic subjects enrolled in the Insulin Resistance Atherosclerosis Study, CRP levels were significantly correlated with BMI, waist circumference, systolic blood pressure, fasting levels of glucose and insulin, indicators of insulin sensitivity, and the number of elements of the plurimetabolic syndrome (Figure 2).\textsuperscript{24} One speculative hypothesis linking impaired insulin sensitivity to enhanced CRP expression stems from a purported diminished physiological immunomodulation of insulin on the transcription of acute-phase plasma protein genes.\textsuperscript{25,26} In the Insulin Resistance Atherosclerosis Study, CRP elevations were inversely related to insulin sensitivity.

In the Mexico City Diabetes Study, baseline levels of CRP, indexes of adiposity, and insulin resistance were evaluated for their predictive value for development of the metabolic syndrome. Over the course of 6 years, 14.2\% of men and 16.0\% of women developed the metabolic syndrome. In women with CRP in the highest tertile, the relative risk for development of the metabolic syndrome and for development of dia-
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The metabolic syndrome has been defined by modestly differing criteria by the third Adult Treatment Panel (ATP III) of the National Cholesterol Education Program, 11 the World Health Organization, 12 and the American College of Endocrinology. 13 The American Diabetes Association and the European Association for the Study of Diabetes developed a position paper concluding that further research is required before this cluster can be managed as a syndrome. In the interim, they recommend that the individual risk factors be evaluated and treated separately. 22 On the other hand, a recent report from the National Heart, Lung, and Blood Institute and American Heart Association (AHA) stated that, considered together, the constellation of symptoms known as the metabolic syndrome is highly predictive of new-onset diabetes. 23

The previously described Italian study 22 used both the World Health Organization and ATP III criteria for metabolic syndrome and found that both definitions identified subjects at greater cardiovascular risk and that neither was superior in predicting cardiovascular risk. Whether any element or elements are considered as fundamental to the definition of this syndrome, some evidence suggests that each element may have a link to inflammation and its indicators. 24 A major opinion adheres to the concept of the metabolic syndrome as a powerful unifying hypothesis of the metabolic factors underlying the development of both atherosclerotic cardiovascular disease and diabetes, 25 whereas another point of view holds that insulin resistance alone is the fundamental feature, and the other clinical elements stem from this metabolic defect. In actual practice, much of this apparent difference may simply be one of emphasis.

**CRP and diabetes**

A growing body of data 24,36 reinforces the concept that inflammation also plays an important role in the pathogenesis of type 2 diabetes and links diabetes with concomitant conditions with inflammatory components. 37 Evidence exists for the prior linkage of euglycemic insulin resistance as a proinflammatory state that may have existed for years before the occurrence of frank type 2 diabetes. 38

Much evidence exists that inflammatory mechanisms play a major role in the cascade of events that results in rupture of atherosclerotic plaque. Upregulation of receptors for advanced glycation end products has been associated with enhanced inflammatory reactions. Increased expression of these receptors has been found to be associated with impaired glycemic control and may be a contributory factor in the complex array of mechanisms that leads to accelerated atherosclerosis in patients with diabetes. 39

In the nearly 6,000 participants in the Cardiovascular Health Study whose circulating levels of inflammatory markers were determined both at baseline and after 3–4 years of follow-up, those who developed diabetes had higher measured levels of CRP than those who remained euglycemic. In addition, those with elevated levels of CRP were found more likely to develop diabetes over the course of the study. 40 In a national survey study, respondents with hemoglobin A1c (A1C) levels ≥ 9% had a significantly higher rate of elevated CRP than those with A1C levels < 7%. This suggests an association between diminished glycemic control and systemic inflammation in people with established diabetes. 41

In a nested case-control study carried out as part of the Women’s Health Study among initially nondiabetic participants who developed diabetes over the course of the study, median baseline levels of IL-6 and CRP were significantly higher among case than among control subjects (P < 0.001), and increasing levels of
both markers were associated with a higher risk of developing diabetes. In this study, increased CRP levels predicted the new onset of diabetes even after adjustment for obesity, coronary risk factors, and fasting insulin levels.

The Monitoring of Trends and Determinants in Cardiovascular Disease Augsburg project involved 2,052 men who were nondiabetic at baseline. During an average follow-up of 7.2 years, 101 cases of diabetes occurred. Participants with CRP levels in the highest quartile had a 2.7-fold greater risk of development of diabetes than those in the lowest quartile. The results of this study suggest the potential involvement of inflammatory mechanisms in the development of diabetes.

Interestingly, the findings of the Strong Heart Study, carried out in an American Indian population with a high prevalence of diabetes, showed that CRP elevations were strongly related to the presence of cardiovascular disease among nondiabetic women but not among diabetic women or among men, irrespective of glycemic status. Thus, the predictive value of CRP elevations may vary among subsets of populations.

CRP in Clinical Practice

Although CRP is only one element of the inflammatory response system, levels of this cytokine reflect the activity of a larger response system. CRP is among the most rapidly acting acute-phase proteins and has a prolonged elimination half-life of ~19 hours. Concentrations of CRP usually appear to rise rapidly in proportion to the degree and severity of inflammatory stimuli. However, thus far, diurnal levels appear to be stable, and CRP concentrations are similarly distributed among men and women, except for women on hormone replacement therapy. These properties of CRP would appear to render this analyte ideal to detect the occurrence of various inflammatory, infectious, and other acute pathological processes. In addition, it is likely that CRP measurements have potential utility for following the activity of certain disease processes and the response to therapeutic interventions.

However, elevations of CRP may be uncommon in the absence of traditional risk factors for CHD. CRP elevations may therefore be attributable to and already accounted for by traditional risk factors. A recent meta-analysis of studies of CRP and other circulating markers of inflammation in CHD risk prediction concluded that CRP may be a somewhat moderate predictor of CHD risk. These data tend to argue against the routine use of CRP measurements for clinical risk assessment in the general population.

The Centers for Disease Control and Prevention and the AHA have published combined evidence-based guidelines for the optimal use of CRP in clinical practice. These guidelines confirm that, although hs-CRP measurement may be useful as an independent marker of prognosis for recurrent events, this analyte should not be used at present for routine screening, and application of secondary prevention measures should not be influenced by hs-CRP determination. However, in intermediate-risk patients without known CHD but with 10-year risk for CHD of 10–20%, the guidelines suggest that measurement of hs-CRP may be considered an independent marker of CHD risk and may be useful, at the discretion of the physician, to help determine optimal treatment. Patients are categorized according to hs-CRP level as follows: <1 mg/l = low risk; 1.0–3.0 mg/l = average risk; and >3.0 mg/l = high risk.

The report of the ATP III panel of the National Cholesterol Education Program also addressed the clinical use of CRP. This report does not recommend routine measurement of CRP for the purpose of modifying LDL cholesterol goals in primary prevention. However, because CRP may have predictive power beyond the classical lipid risk factors, this report indicates that some investigators consider lowering LDL cholesterol more aggressively in adults with elevated levels of CRP than may otherwise be indicated by an evaluation solely of the major risk factors. The 2004 update to the ATP III guidelines also suggests that CRP measurements may be useful as a guide to treatment targets. Thus, a patient with an hs-CRP > 3 mg/l would be allocated to the moderately high-risk category for cardiovascular disease, even with unremarkable lipid levels.

Management Considerations

Strategies that target obesity and insulin resistance, when found to be effective, may ameliorate both endothelial dysfunction and low-grade inflammation and have the theoretical potential to decelerate or prevent the occurrence of type 2 diabetes and cardiovascular disease. Pharmacological and lifestyle interventions may reduce both the risk for CHD and levels of CRP, if elevated. However, convincing evidence does not as yet exist to indicate that modalities directed toward lowering of circulating levels of CRP can reduce the occurrence of cardiovascular events.

Peroxisome proliferator-activated receptor agonists may improve insulin sensitivity and glycemic control in patients with type 2 diabetes and cardiovascular disease. These agents have reduced clinical inflammatory responses and have possibly been responsible for a trend toward reduced coronary events in a large randomized clinical trial. Etaenecot, a TNF-α agonist, produced significant reductions in CRP compared with placebo (~2.4 vs. 0.5 mg/l, \(P < 0.001\)) and improved other inflammatory markers (including fibrinogen, IL-6, and adiponectin) in patients with the metabolic syndrome in a recent randomized trial.

Results of recent studies also suggest a potential association between lower CRP levels and improved clinical outcomes with statin therapy.
Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm—patients with baseline levels of LDL cholesterol in the intermediate range (mean ~ 130 mg/dl) showed further reduction of risk with statin therapy. Statins, which may have anti-inflammatory effects, under various clinical conditions have produced significant reductions in CRP levels. In the Cholesterol and Recurrent Events trial of secondary prevention, patients treated with pravastatin who had higher hs-CRP levels at baseline appear to have experienced a much greater reduction in relative risk of recurrent clinical events than those with lower hs-CRP levels (54 vs. 25%, respectively), although the two groups had similar baseline lipid profiles. In the Air Force/Texas Coronary Atherosclerosis Prevention Study of primary prevention, lovastatin therapy was effective in reducing cardiovascular events in patients with hs-CRP levels above the median, even in those with LDL cholesterol levels below the median. In both trials, reductions in levels of hs-CRP appeared to be independent of reductions in levels of LDL cholesterol. The above-mentioned findings, while intriguing, must be interpreted with caution because the data were derived from post hoc analyses and also involve rather small numbers of cardiovascular events.

The Justification for the Use of Statins in Primary Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) is an ongoing, randomized, placebo-controlled trial that seeks to evaluate whether long-term aggressive therapy with rosuvastatin, 20 mg/day, for 3–4 years can prevent first major cardiovascular events in an apparently healthy population of adult men and women with unremarkable levels of LDL cholesterol (< 130 mg/dl) but with potentially increased risk for CHD due to elevated levels of hs-CRP (≥ 2 mg/l). JUPITER investigators will enroll ~ 15,000 middle-aged men and women. The JUPITER trial has been designed to test the potential utility of rosuvastatin therapy to diminish the occurrence of type 2 diabetes. If positive, the findings are likely to elevate the role of CRP both as a risk factor and, more importantly, a treatment target in the presence of average concomitant serum levels of LDL cholesterol. Moreover, a positive outcome in this important clinical trial would likely require an urgent reassessment of risk stratification, use of statin therapy, and treatment goals for LDL cholesterol and other lipoprotein lipid end points. In all likelihood, a demonstration of the need for intensification of therapy for patients previously considered to be at lower CHD risk will result.

Conclusions
Current opinion varies widely on the additive value of CRP testing for cardiovascular risk assessment. Debates continue for and against the use of CRP measurements as a part of screening for global risk assessment. A Scientific Statement from the AHA/centers for Disease Control and Prevention recommended use of such testing in certain population groups but stated that the benefits of a treatment strategy based on such measurements remain uncertain.

However, with the metabolic syndrome and diabetes, the role of inflammation and of CRP as a marker of inflammation appear less controversial. There is increasing evidence that inflammation underlies both the metabolic syndrome and diabetes and may predict both. The role of lowering CRP in reducing the risk for and improving the prognosis of diabetes is undergoing assessment.

The results of ongoing clinical trials will continue to provide data on the additive value of testing levels of CRP and other inflammatory markers for cardiovascular risk assessment and should delineate the clinical utility of such testing in various disease states.

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