Editorial

Inflammation, Metabolic Syndrome, and Diet Responsiveness

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There has been a surge of interest in the role of inflammation in causation of atherosclerosis and acute coronary syndromes. This interest is spurred both by pathological studies showing that ruptured coronary plaques manifest inflammatory characteristics and by the demonstration that inflammatory biomarkers in the plasma correlate with risk for acute coronary syndromes. Among the biomarkers that correlate with acute coronary syndromes, the most robust is C-reactive protein (CRP). The liver is known to respond to high levels of cytokines in the circulation with an increased production of CRP. A recent report by the American Heart Association/Centers for Disease Control and Prevention (AHA/CDC) indicated that CRP measurements may provide incremental information for global risk assessment for coronary heart disease beyond that obtained from established risk factors. These measurements can be made at the discretion of physicians, provided that established risk factors are given priority in global risk assessment.

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Another recent observation of significance is that elevated CRP levels associate with the metabolic syndrome. The latter is a syndrome in which several metabolic risk factors cosegregate in one person. Risk factors of the metabolic syndrome include atherogenic dyslipidemia (raised triglycerides, elevated apolipoprotein B, small LDL particles, and low HDL cholesterol), elevated blood pressure, insulin resistance (glucose intolerance), a proinflammatory state, and a prothrombotic state. Several studies add support to the concept that a proinflammatory state is one component of the metabolic syndrome. Ridker et al have confirmed that elevated CRP associates strongly with metabolic syndrome risk factors; moreover, these workers reported that high CRP levels impart risk for major coronary events beyond that imparted by the other metabolic risk factors. The reasons for a link between inflammation and metabolic syndrome are not fully understood. One explanation may be that adipose tissue in obese persons with the metabolic syndrome releases increased amounts of cytokines into the circulation; this in turn accounts for a greater production of CRP by the liver. Another possibility is that insulin resistance per se is responsible for a higher production of cytokines. Regardless of mechanism, the finding that patients with metabolic syndrome exhibit characteristics of a proinflammatory state provides a new and exciting connection between inflammation and metabolic processes. This connection promises to yield new insights into pathways whereby the metabolic syndrome leads to atherosclerosis and acute coronary syndromes. Undoubtedly, the connections between inflammation and metabolism are complex and present a challenge for new research.

One area of this association is explored by Erlinger et al in the present issue of Circulation. These authors examined the effects of a therapeutic dietary pattern named Dietary Approaches to Stop Hypertension (DASH) on plasma lipids and lipoproteins in persons with varying levels of serum CRP. The DASH diet is primarily designed to lower blood pressure. Because of its nutrient composition, the DASH diet seemingly reduces blood pressure independently of its sodium content. It makes use of high intakes of fruits and vegetables (total of about 9 servings per day), low-fat dairy products, and other reduced-fat foods. The diet used in the study by Erlinger et al provided about 27% of total energy as fat, 6% of energy from saturated fatty acids, and 151 mg/d of cholesterol. Besides lowering blood pressure, the DASH diet previously has been shown to reduce plasma lipids. In fact, there are many similarities to the therapeutic diet recommended by the National Cholesterol Education Program (NCEP) for treatment of high blood cholesterol. However, there are some differences in that the DASH diet puts more emphasis on consumption of fruits and vegetables and low-fat dairy products than does the NCEP diet. Nonetheless, both diets are equally low in saturated fatty acids and cholesterol, which accounts for their favorable effects on LDL cholesterol levels.

In the study of Erlinger et al, the DASH diet was compared with a diet that contained 37% of energy from total fat and 16% from saturated fat. A majority of subjects were African-American women who were either overweight or obese. The prevalence of the metabolic syndrome is known to be high in obese African-American women. Even so, in the present study, mean plasma triglycerides and LDL cholesterol levels were relatively low (ie, about 85 mg/dL and 126 mg/dL, respectively). One point to make is that few subjects in this study had categorical dyslipidemia, so whether the results can be extrapolated to other population groups or to those with various forms of dyslipidemia remains to be determined.
The major finding from Erlinger et al\textsuperscript{12} was that persons with higher levels of CRP failed to respond favorably in plasma lipid levels to the DASH diet when compared with those with lower CRP levels. Total cholesterol and LDL cholesterol concentrations fell on the DASH diet when CRP levels were low but not did not fall much—if at all—when CRP levels were high. Triglyceride reductions likewise were greater when CRP levels were low. Therefore, it must be said at the outset that the results of this study are of interest. There has been a long history to the investigation of factors that influence variation in responsiveness of plasma lipids to dietary change. These factors have been reviewed in detail by Denke et al\textsuperscript{15,16}; differences in genetic makeup, adherence to dietary change, body fat content, and lipoprotein kinetics have all been implicated as factors affecting diet responsiveness. Erlinger et al\textsuperscript{12} add a new factor to this list—namely, elevated CRP. The results of the article by Erlinger et al\textsuperscript{12} naturally raise the question of mechanism. What are the reasons for a relationship between CRP concentrations and dietary responsiveness? According to the authors, because of a limitation in sample size, they were not able to examine higher-order relationships that might provide useful information about mechanism. Consequently, we are left with speculation. Even so, it may be of interest to consider possible reasons underlying the observations of this report.

The authors speculate that an inflammatory state prevents a favorable responsiveness in serum lipids to the DASH diet. Whether other features of the metabolic syndrome also correlate with a lack of response was not explored. Nonetheless, because high concentrations of CRP typically reflect an increase in circulating cytokines, we must ask whether cytokines themselves might alter the metabolism of lipoproteins in a way that will interfere with the actions of dietary change to produce a reduction in lipid levels. For example, high levels of tumor necrosis factor-\(\alpha\) have been reported to interfere with the action of lipoprotein lipase, which in turn contributes to hypertriglyceridemia.\textsuperscript{17,18} It also is theoretically possible that cytokines might interfere with the expression of LDL receptors; if so, the result could be higher levels of plasma LDL cholesterol and a failure to respond to dietary change. To date, however, such effects of cytokines have not been reported. Certainly, patients with severe inflammatory conditions do not have elevated LDL cholesterol concentrations; moreover, cytokine administration does not raise LDL levels.\textsuperscript{18}

Two major causes of CRP variations are cigarette smoking and obesity.\textsuperscript{2} Because the number of smokers in this study was low, it is unlikely that smoking was a significant factor that can explain the observed variation in CRP. The question of obesity is more germane. Body weight is perhaps the major source of variation in CRP levels in the population.\textsuperscript{19,20} This possibility was not discussed in any detail by the authors. However, it seems very possible that more-obese persons, who have higher CRP levels, will be less responsive to dietary change. Previous reports support the concept that obesity mitigates the response of serum total cholesterol and LDL cholesterol to dietary change.\textsuperscript{15} The reasons for this interference are not known. Elevations of circulating cytokines might be one factor, but other features of the metabolic syndrome could be involved as well.

An interesting family study of responsiveness of plasma lipids to type of dietary fat was reported recently by Denke et al.\textsuperscript{16} This study employed unsaturated fat as the dietary modality for lipid lowering. The results of the study by Denke et al\textsuperscript{16} are instructive as to the complexity of the overall issue of diet responsiveness. In this report,\textsuperscript{16} statistical correlations between different factors and variability of responsiveness to different factors were examined. Erlinger et al\textsuperscript{12} carried out no such correlations to determine the strength of the association. Denke et al\textsuperscript{16} found that body mass index predicted response; i.e., heavier persons had higher LDL cholesterol levels and less LDL-lowering in response to dietary change than did lean individuals. Other factors identified to be affecting response were family membership and the change in the ratio of linoleic acid to oleic acid in plasma cholesterol esters.

There has been a longstanding interest in the possibilities that differences in responsiveness in plasma LDL cholesterol concentrations can be explained to a large extent by genetic factors. Much of the interest has focused on factors affecting differences in response to change in dietary cholesterol. Many studies in laboratory animals, especially in primates, have demonstrated that there are high and low responders to changes in cholesterol intakes. Although metabolic studies have been carried out in animals to localize the “defect” responsible for hyperresponsiveness to dietary cholesterol, a definitive result has not been obtained. Likewise, single major genes for hyperresponsiveness have not yet been identified in primates in spite of considerable investigation. Previously, Beynen and Katan\textsuperscript{21} performed studies that revealed the complexity of the diet-responsiveness issue. These workers performed repeat studies to determine reproducibility of patterns of dietary response in individuals fed high-cholesterol diets. One important finding was a variable reproducibility in the pattern of response. On one occasion, a higher responder became a low responder, and vice versa. These studies add a note of caution for any reports of consistency of dietary responsiveness to serum lipids for individuals. Repeat studies in individual subjects may not give the same results, which could make genetic studies of diet responsiveness in humans problematic. Erlinger et al\textsuperscript{12} suggest that CRP levels could be used as an indicator of who will be responsive to dietary change in the clinical setting. This in fact may not be the case. Although multiple factors have been associated with a relative diet nonresponsiveness in groups, individual variation in responsiveness is such that accurate prediction will be difficult if not impossible when applied to individuals.

The present study by Erlinger et al\textsuperscript{12} is of interest because it reveals a new association between a serum inflammatory marker and responsiveness of serum lipids to dietary change. The study calls for further investigation to delineate the nature of the relationship. However, it cannot yet be concluded that a subclinical state of inflammation is a direct cause for the diminution of responsiveness of serum lipids to dietary change. Future studies will require that various...
components of the metabolic syndrome be examined for their contribution to diet responsiveness.

References

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