Inflammation and Diabetic Vascular Complications

During the past decade, epidemiology has emerged as a science of critical importance to our understanding of diabetes and its complications. *Diabetes Care* has become a leading vehicle for transmitting to its readers new epidemiologic knowledge about diabetes and its complications. In this issue, Ford (1) has analyzed results from the third and most recent National Health and Nutrition Examination Survey (NHANES III), in which clinical examinations and laboratory evaluations were done on 20,050 people (≥17 years of age) between 1988 and 1994 in the U.S. In the past, these surveys have provided excellent objective information about the health of U.S. citizens, and the results have influenced health policies for people with diabetes and other disorders.

Recognizing that levels of plasma C-reactive protein have been reported to be elevated in obese people, Ford analyzed results from the 15,569 participants in NHANES III who had BMI and C-reactive protein levels measured. This provided clear evidence of a relationship between BMI and plasma C-reactive protein levels. Some appreciation of the magnitude of the effect of BMI can be noted from the observation that 26–51% of participants with BMI >30 kg/m^2 had C-reactive protein levels elevated above the 85th percentile of normal. A small sample of people with BMI >40 kg/m^2 had C-reactive protein levels six times greater than those with BMI <25 kg/m^2. The associations held after exclusion of people with diabetes and other diseases that could affect C-reactive protein levels. Among the 10,055 participants in whom fasting glucose and C-reactive protein levels were obtained, there was no significant elevation of C-reactive protein in subjects with impaired fasting glucose (110–125 mg/dl), but there were significant elevations in newly discovered diabetic subjects (fasting glucose ≥126 mg/dl) and in previously diagnosed diabetic individuals. Approximately 17% of the participants had diabetes using these criteria. From 34 to 39% of people with diabetes had elevated C-reactive protein levels, and this association was not completely explained by increases in BMI.

It must be recognized that there are many possibilities that could explain Ford's findings of elevated C-reactive protein levels in individuals with diabetes or elevated BMI. There are many potential stimuli to the production of acute-phase proteins by the liver. Chronic inflammation is a leading candidate, and it is difficult to recognize and to exclude in a large population study such as NHANES III. For instance, one hidden source of infection quite common in diabetes is periodontal disease. Obese individuals have an increased risk for active gallbladder and cardiovascular disease, either of which could elevate C-reactive protein levels in plasma.

Why would anyone do such exhaustive analyses of this large data set to explore these specific correlations? There was a good rationale, and a history of interest in this area dating back at least 30–40 years. It has long been recognized that there are a number of acute-phase proteins produced by the liver in response to a wide variety of stimuli, including infection, inflammation, tissue injury, and neoplasia (2). These have been termed acute-phase reactants (2). Examples include C-reactive protein, fibrinogen, α-1 antitrypsin, plasminogen activator inhibitor 1 (PAI-1), sialic acid, and certain components of the complement system. In early work by McMillan (3), he found that progressive increases in plasma levels of C-reactive protein, α-1 glycoprotein, haptoglobin, and plasma viscosity correlated with increasing evidence of microangiopathy in type 2 diabetic subjects.

C-reactive protein has been identified in some studies as a risk marker for cardiovascular disease. In the U.S. Physicians Health Study, baseline plasma levels of C-reactive protein predicted the risk of future myocardial infarction and ischemic stroke (4). In the quartiles with the highest C-reactive protein levels, the relative risk for myocardial infarction was increased almost threefold, and that for ischemic stroke almost twofold, when compared with the lowest quartiles. Randomization to low-dose aspirin therapy (325 mg every other day) led to a 55% reduction in the risk for a subsequent myocardial infarction (P = 0.02). An anti-inflammatory mechanism was suggested. Recently, there has been renewed interest in the inflammatory hypothesis as an underlying mechanism of arterial injury. Many organisms, including *Chlamydia pneumoniae*, *Helicobacter pylori*, herpes simplex, and cytomegalovirus, have been postulated as sources of chronic inflammation of the vasculature (4). Pickup et al. (5) have postulated that syndrome X and type 2 diabetes may be manifestations of an ongoing acute-phase response that may represent a chronic adaptation of the immune system. They found increases in plasma levels of sialic acid and α-1 glycoprotein in type 2 diabetes, and the highest values in patients with syndrome X. Recognizing that interleukin (IL)-1 and IL-6 may be mediators of the acute-phase response from the liver, they also studied plasma IL-6 levels and found them to be elevated in both diabetic groups.

Two acute-phase proteins, fibrinogen and PAI-1, are also risk markers for coronary artery disease and may be elevated in the plasma of people with type 2 diabetes and/or syndrome X. It is of interest that another inhibitor of plasminogen activator, α-1 antitrypsin, is also an acute-phase reactant that may be elevated in the plasma of people with diabetes. Along with alterations of platelet behavior and of the intrinsic coagulation system in diabetes, it is now reasonable to hypothesize that a prothrombotic state exists, even in the early stages of type 2 diabetes (6). If this state of affairs were chronic, it could help explain the increased incidence of vascular thrombosis in people with type 2 diabetes.

The overweight and diabetic participants in the present study were strong candidates for ongoing vascular injury. Pickup et al. (5) provided evidence that one marker of vascular injury, urinary albumin, correlated with elevated acute-phase proteins in type 2 diabetes and in syndrome X. In people with type 2 diabetes, urinary albumin is a predictor of cardiovascular events. In addition, recent studies have shown that impaired glucose tolerance is a better predictor of cardiovascular events than impaired fasting glucose (7). It is likely

that if either urinary albumin or impaired glucose tolerance had been reported in the present study, elevations of C-reactive protein may have correlated with either or both of these risk markers.

If one were to postulate that these correlations between acute-phase reactants and obesity, syndrome X, and type 2 diabetes reflect vascular disease, what sequence of events might be occurring? Insulin resistance may be the common denominator. Plasma tumor necrosis factor (TNF)-α and IL-6 levels may be elevated in obesity and diabetes, two insulin-resistant states. TNF-α has been shown to cause insulin resistance, and IL-1, IL-6, and TNF-α may stimulate the release of adhesion molecules in the vasculature. This response may cause smooth muscle cell proliferation and endothelial permeability, two early manifestations of arterial damage. Hyperglycemia may lead to the production of advanced glycation end products, which stimulate macrophages and lymphocytes to secrete cytokines. These cytokines (IL-1 and IL-6), in turn, act on the liver to increase production of acute-phase reactants, which may increase blood viscosity, activate the intrinsic coagulation system, alter platelet behavior, and/or inhibit lysis of the fibrin clot. Further, it has been demonstrated in animals and humans that the acute-phase response is associated with an increase in plasma levels of VLDL and a decrease in HDL cholesterol, two major components of diabetic dyslipidemia. Thus, one can correlate many aspects of atherosclerosis and thrombosis with the acute-phase reaction in obesity, type 2 diabetes, and syndrome X. Longitudinal studies are needed to explore the sequence of events.

Whatever the time course and mechanisms involved, it is clear that work such as that reported by Ford (1) should stimulate investigators to respect the magnitude of tissue damage that may occur in obesity, type 2 diabetes, and syndrome X from an activated acute-phase response system. Future work will identify the sequence of events during the course of these disorders. New information will emerge that should guide therapeutic approaches to the devastating problem of accelerated cardiovascular disease in obesity, syndrome X, and type 2 diabetes.

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