Coronary Disease in Type 1 Diabetes

Causal contiguity and clinical implications

Orchard et al. (1), in this issue of *Diabetes Care*, have provided valuable insights and illuminated pathophysiologic mechanisms underlying coronary artery disease associated with type 1 diabetes. All 603 patients studied were initially free from clinically overt coronary artery disease. Somewhat surprisingly, however, elevations of concentrations of HbA_{1c} in blood were not descriptors of subsequent coronary events. The authors concluded that "greater glycemia does not seem to predict future coronary events." Thus, although glycemic control may not be the key to reduction of coronary risk, favorable modification of a key factor that was identified, i.e., insulin resistance, may.

Hyperglycemia is, of course, not only the hallmark of type 1 and type 2 diabetes but also its defining feature. Glycemic control is imperative to prevent or retard microvascular complications associated with both types of diabetes. Subjects with either type 1 or type 2 diabetes exhibit increased concentrations of fibrinopeptide A in blood and urine, reflecting thrombin activity in vivo, indicative of activation of the coagulation system, compared with concentrations in nondiabetic subjects. Their platelets exhibit increased reactivity. Decreased platelet membrane fluidity, potentially reflecting increased glycation of platelet membrane proteins, may contribute (2). Endothelial cell function in vitro and in vivo is affected adversely. Advanced glycation end products (AGEs) in vessel walls may impair vasodilatory capacity. Such factors may contribute to the increased cardiovascular risk incurred by those with type 1 diabetes. Yet, as Paul Harvey would say, we must consider "the rest of the story."

As pointed out by Dr. Lebovitz (3), "from the perspective of cardiovascular disease, a. . . sensible way to classify diabetes mellitus is to define two variants. One in which there is no significant insulin resistance and the other in which insulin resistance is a dominant pathophysiological abnormality." Coronary risk factors including elevated LDL, diminished HDL, impaired fibrinolysis, increased BMI, and hypertension do cluster in association with insulin resistance. In contrast to the typically prompt appearance of coronary disease after onset of type 2 diabetes, in type 1 diabetes its appearance usually occurs only after diabetes has been present for many years or decades. Results in a large cross-sectional study of >3,000 patients with type 1 diabetes (4) showed that cardiovascular disease is presaged by dyslipidemia, hypertension, and increased BMI but not by elevated concentrations of HbA_{1c} in blood.

Insulin resistance and diabetes

Himsworth, in the 1930s, performed what have been referred to by Dr. Gerald Reaven (5) as "a series of simple, but elegant experiments aimed at understanding" the causes of hyperglycemia in patients with diabetes. His observations led him to propose that "the diminished ability of tissues to utilize glucose is referable to either a deficiency of insulin or an insensitivity to insulin, although it is possible that both factors may operate simultaneously." Dr. Reaven and others identified insulin resistance as the link between type 2 diabetes and malignant coronary disease. In fact, even without diabetes, insulin resistance accelerates coronary disease (6).

Some patients with brittle type 1 diabetes, marked microvascular disease with nephropathy and retinopathy, and poorly controlled hyperglycemia remain remarkably free from overt coronary artery disease, even at a relatively advanced age. Conversely, many patients with "mild" type 2 diabetes, i.e., well-controlled hyperglycemia, manifest relentless progression of accelerated coronary artery disease and its sequelae. Control of hyperglycemia markedly diminishes microvascular complications of type 2 diabetes but only modestly diminishes macrovascular manifestations.

In type 2 diabetes the frequent occurrence of cardiac events despite the absence of premonitory abnormalities detectable with exercise stress tests or reflected by exertional angina is all too typical. Accordingly, cardiologists have had little difficulty accepting the concept that "something else" besides carbohydrate intolerance is a major contributor to the relation between diabetes and acceleration of coronary artery disease. That "something else" appears to be insulin resistance, perhaps mediated in part by consequences of compensatory hyperinsulinemia and hyperproinsulinemia. For diabetologists experienced with the life-saving use of insulin, it has been difficult to view hyperinsulinemia as a potential culprit. Thus, the possibility that insulin resistance and excess insulin, even when compensatory, could be deleterious has itself been resisted.

Insulin resistance and coronary disease

Derangements in the coagulation and fibrinolytic systems and in platelet function appear to be mediated in patients with type 2 diabetes in part by insulin resistance and perhaps hyperinsulinemia and hyperproinsulinemia (2). Such derangements are also seen in first-degree nondiabetic relatives of subjects with type 2 diabetes. Decreased fibrinolytic system capacity is observed consistently in association with type 2 diabetes (2) and even in association with insulin resistance in the absence of diabetes. It is attributable to augmented concentrations in blood of circulating plasminogen activator inhibitor type-1 (PAI-1), a marker of increased risk of acute myocardial infarction and a protein exhibiting increased expression in response to exposure of diverse cell types to insulin and proinsulin as well as free fatty acids and angiotensin II and IV (7).

Because of the potential impact of PAI-1 on cell migration influencing the nature of evolving atheroma, potentially rendering them particularly vulnerable to rupture, and because increased PAI-1 is

strongly associated with insulin resistance and compensatory hyperinsulinemia, PAI-1 has been implicated in accelerating development of coronary plaques that precipitate acute coronary syndromes (8). Inflammation is known to be associated with insulin resistance. It and cytokines associated with it can contribute to a prothrombotic state.

On purely statistical grounds, one would anticipate insulin resistance in many people with type 1 diabetes. In addition, however, intensive treatment of type 1 diabetes appears to increase central obesity. In fact, it has been noted that "insulin treatment of type 1 diabetic patients creates the insulin resistance syndrome in a significant number" (3).

The compelling observations reported by the Pittsburgh Epidemiology of Diabetes Complications Study Group implicate insulin resistance as a major determinant of acceleration of coronary artery disease associated with diabetes. The striking association of apparent insulin resistance with subsequent coronary events and the striking lack of an association of elevated HbA_{1c} with subsequent events put the issue in bold relief. Stringent control of hyperglycemia is imperative with diabetes of any type to retard the evolution of nephropathy, neuropathy, retinopathy, and metabolic derangements contributing to macroangiopathy. As noted (1), hyperglycemia "merits close control for the prevention of microvascular complications." Determinants of insulin resistance may directly and adversely affect vessels. Thus, insulin resistance and accelerated coronary artery disease may have common biochemical ancestors. Alternatively, insulin resistance itself may accelerate coronary disease. It is possible that the compensatory hyperinsulinemia may exert deleterious effects on vessels (8).

Because insulin resistance can be modified favorably with interventions readily available to clinicians, we should heed the admonition "to address traditional risk factors including insulin resistance" (1) in our efforts to prevent and retard the progression of coronary artery disease. Himsworth was certainly right. Yet, with respect to coronary disease, both types of diabetes may meld. The insulin resistance underlying type 2 diabetes and frequently manifested in those with type 1 diabetes may be the most powerful determinant of coronary disease and its sequelae and a culprit most amenable to favorable modification with consequent reduction of the toll from coronary artery disease.

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