Acceleration of Restenosis by Diabetes
Pathogenetic Implications

Burton E. Sobel, MD

Van Belle et al, who were among the first to emphasize the potential importance of diabetes in adverse late outcomes after percutaneous coronary interventions (PCI), provide useful observations in their present study of a large cohort of diabetic patients who were treated with standard balloon angioplasty, scheduled for repeated angiography 6 months later, and followed for an average of 6.5 years. They conclude that the incidence of both nonocclusive and occlusive restenosis is higher in diabetic subjects as judged from comparison with historical control subjects. Furthermore, they report that occlusive restenosis is “a strong, independent correlate of long-term mortality.” These results implicate accelerated restenosis as both a consequence of diabetes and a cause for increased mortality after PCI in diabetic patients. They are consistent with results in prospective, long-term–mortality, controlled trials and with results in observational mortality and angiographic studies.

Observations such as those reported by Van Belle et al raise important clinical questions. One is whether either surgery or PCI is a preferred initial treatment strategy for patients with diabetes who require coronary revascularization. The advent and wide utilization of stents, powerful antiplatelet agents, and technological advances after enrollment in the studies cited above had been largely completed makes extrapolation difficult and precludes a definitive answer. However, stenting does not obviate accelerated restenosis with diabetes even though it reduces its incidence in some patients and in some types of vessels. Furthermore, in patients with diabetes who sustain myocardial infarction after previous, remote revascularization, mortality is lower when the antecedent intervention has been CABG compared with PCI.

Another question that arises from observations such as those of Van Belle et al is whether the nature of management of diabetes per se influences the incidence and severity of restenosis. Adverse outcomes after PCI have been related not only to the presence of diabetes but also to the use of insulin or oral hypoglycemic agents, particularly sulfonylureas, which were the only commercially available agents in the United States until relatively recently.

The association of adverse outcomes with the nature of treatment of diabetes in addition to that with diabetes itself could be a reflection of greater severity or duration of the disorder in those who develop a higher incidence of adverse outcomes. Alternatively, a body of compelling information indicates that deleterious effects of insulin or proinsulin on native vessel walls and on vessels subjected to PCI may account for a higher incidence of adverse outcomes after PCI in patients with diabetes who are treated with insulin or oral agents compared with those who are treated with dietary management and exercise alone. This possibility is supported by results in 2 small studies in which a regimen with an insulin sensitizer (troglitazone) compared with one devoid of a sensitizer but yielding comparable glycemic control decreased carotid intimal medial thickness in diabetic subjects in one study and improved the outcome of coronary stenting in another.

It has become increasingly clear that type 2 diabetes, by far the most prevalent form in adults, is a disease of dysinsulinemia. For as long as 10 years before the appearance of frank carbohydrate intolerance, afflicted subjects are hyperinsulinemic. It is only when pancreatic beta cell “exhaustion” supervenes that impaired glucose tolerance and frank diabetes evolve. Ultimately, “glucotoxicity” and the continued exhaustion of pancreatic beta cells result in absolute insulin deficiency.

Although maintenance of adequate concentrations of insulin in blood is necessary for euglycemia and avoidance of hyperlipidemia, both profoundly important determinants of morbidity and mortality in patients with diabetes, the dysinsulinemia has been implicated in contributing to macrovascular disease and particularly coronary artery disease and its sequelae, acute coronary syndromes. The observations in the clinical studies cited above are consistent with this possibility, as is the fact that hyperinsulinemia and insulin resistance by themselves, even in subjects who are not diabetic, are associated with an increased incidence of coronary events among patients stratified with respect to the presence or absence of hyperlipidemia and other independent determinants of coronary disease. Furthermore, subjects with insulin resistance who are not diabetic, including women with the polycystic ovarian syndrome and patients with metabolic syndrome X characterized by hypertriglyceridemia, hypertension, abdominal obesity, increased intra-abdominal fat, and impaired fibrinolytic capacity are at increased risk of coronary events.

The lack of a striking decrease in macrovascular as opposed to microvascular disease in the Diabetes Control and

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Complications Trial (DCCT)\textsuperscript{15} and the United Kingdom Prospective Diabetes Study (UKPDS)\textsuperscript{16} is consistent with the impact of factors other than glycemic control and normalization of hyperlipidemia on coronary risk in patients with type 2 diabetes.

Deleterious effects of insulin, proinsulin, or both leading to accelerated macroangiopathy in type 2 diabetes alone or in association with elevated concentrations of free fatty acids and VLDL in blood may result from abnormalities in platelet activation,\textsuperscript{17} the coagulation system,\textsuperscript{18} the fibrinolytic system in blood,\textsuperscript{19,20} and the proteo(fibrino)lytic system in vessel walls.\textsuperscript{21} Derangements in these systems can accelerate the evolution of macroangiopathy by exposing luminal surfaces of vessel walls to clot-associated mitogens and atherogenic stimuli. Thus, it is not necessarily surprising that restenosis is accelerated in patients with type 2 diabetes.

Van Belle et al were very careful to write that occlusive restenosis was a “correlate” of long-term mortality.\textsuperscript{1} They did not write that it was a determinant of long-term mortality. In fact, the increased mortality seen in patients exhibiting occlusive restenosis may have been a consequence of the nature of the restenotic lesion rather than or as well as of the phenomenon of occlusion itself.

In vessels in nondiabetic experimental animals, stenting leads to neointimal formation mediated through transient neointimal migration and proliferation of vascular smooth muscle cells, as well as changes in the phenotype of the stimulated vascular smooth muscle cells from a contractile to a proliferative phenotype.\textsuperscript{22} Paradoxically, decreased atherosclerotic plaque mass has been observed in insulin-treated diabetic subjects, a phenomenon that was considered to reflect “impaired adaptive remodeling or shrinkage of arterial wall, of plaque, or of both.”\textsuperscript{23} In diabetic subjects whose vessels exhibit restenosis after PCI, “intimal hypercellular tissue content is reduced in restenotic tissue” compatible with phenomena other than a proliferative response of vascular smooth muscle cells.\textsuperscript{24} We have observed increased intramural synthesis of plasminogen activator inhibitor type-1 (PAI-1) in the walls of vessels in experimental animals subjected to balloon angioplasty. We have found also that insulin stimulates PAI-1 synthesis by stabilizing PAI-1 mRNA in human cells in culture, in adipocytes, and in vessel walls in vivo.\textsuperscript{25} Thus, the nature of the restenotic lesion in diabetes may be dominated by inhibition of proteolysis by PAI-1 during evolution of the lesions, accumulation of extracellular matrix and lipid, and a paucity of vascular smooth muscle cell migration and proliferation typical of vascular smooth muscle cell–rich atherosclerotic lesions and restenosis under other conditions.

This possibility may contribute to increased mortality in diabetic patients with restenosis through a mechanism implicated in the high incidence of acute coronary syndromes in patients with diabetes who have not been subjected to PCI.\textsuperscript{21} Because proteolysis in macrophages in shoulder regions of mature plaques is pivotal in precipitation of acute coronary syndromes\textsuperscript{26} secondary to rupture of the vulnerable plaques,\textsuperscript{27} it is not immediately obvious how increased intramural PAI-1 and decreased proteo(fibrino)lysis in vessel walls could account for an increased incidence of acute coronary syndromes. However, PAI-1 is increased in the coronary atheroma from diabetic subjects.\textsuperscript{28} The inhibitor appears likely to alter the biochemical composition of plaques as they evolve. Inhibition of vascular smooth muscle cell migration to the neointima in such evolving plaques in the presence of atherogenic stimuli such as oxidized LDL and the diminution of plasmin-dependent activation of extracellular matrix metalloproteinases may lead to development of plaques that are characterized by increased ratios of lipid to vascular smooth muscle cell, an increased content of extracellular matrix, and thin fibrous caps—hallmarks of plaque vulnerability.\textsuperscript{25,27} If directionally similar changes are typical of the accelerated restenosis seen in diabetic subjects as suggested by results from others,\textsuperscript{24} the associated increased mortality may be reflective of the vulnerability to rupture of plaques in restenotic regions secondary in part to their modified biochemical composition in addition to their contributions to mechanical obstruction of coronary blood flow.

Reduction of hyperinsulinemia and of PAI-1 concentrations in blood has been demonstrated with the use of insulin-sensitizing regimens.\textsuperscript{29–31} If intramural PAI-1 can be diminished by the same approach in evolving restenotic lesions, the result may be formation of lesions less prone to rupture and hence less prone to precipitate acute coronary syndromes and death.

The Bypass Angioplasty Revascularization Investigation (BARI) II trial, about to be initiated, will test this hypothesis by randomizing diabetic subjects who have undergone diagnostic coronary angiography to 2 different types of treatment regimes for management of the diabetes. One, an insulin-sparing regimen, will entail reliance on the use of insulin sensitizers such as thiazolidinediones and metformin. The other, an insulin-providing regimen targeting the same efficacy of glycemic control, will entail reliance on the use of sulfonylureas and insulin.

The possibility that the dysinsulinemia of type 2 diabetes is pivotal in the evolution of vulnerable plaques and restenotic lesions must not detract from cardinal principles in the management of patients with diabetes and coronary artery disease. The primacy of glycemic control must not be forsaken in view of its clear deterministic link to nephropathy, neuropathy, and retinopathy. Coronary risk factor reduction, including control of hyperglycemia, hyperlipidemia, and hypertension, and smoking cessation are imperative. The potential value of antioxidants should be considered in view of the oxidative stress demonstrably present in association with diabetes and the possibility of oxygen-centered radical contributions to vasculopathy.

Patients with diabetes who develop myocardial infarction should be treated vigorously to induce glycemic control. ECG criteria of amelioration of myocardial manifestations of myocardial ischemia were recognized by Sodi-Pallares et al\textsuperscript{32} many decades ago. Myocardial preservation inducible with glucose, insulin, and potassium\textsuperscript{33} was demonstrated later. Both have been largely neglected until recent observations in the DIGAMI study.\textsuperscript{34} These results are consistent with preservation of jeopardized myocardium in patients with diabetes by optimization of metabolism in ischemic zones.
with “insulin-glucose infusion initiated as soon as possible after onset of myocardial infarction.”

The study of inborn errors of metabolism attributable to mendelian dominant or recessive traits such as phenylketonuria and adenosine deaminase deficiency has provided profound support for the 1 gene–1 protein hypothesis and clarified mechanisms by which derangements in synthesis of a specific protein produce disease. It has also opened the door to gene therapy. Disorders such as atherosclerosis and diabetes are multifactorial and multigenic. Insight into their pathogenesis comes largely from careful clinical observations such as those by Van Belle et al and delineation of biochemical mediators influencing lesion development. Pathogenetic implications of accelerated restenosis and increased mortality after PCI in patients with diabetes are likely to be relevant also to atherosclerosis in nondiabetic subjects.

References
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