Editorial

Vascular Thrombosis in Type II Diabetes Mellitus

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One prevailing point of view is that many individuals with established type II diabetes have gone through years of impairment of glucose tolerance and hyperinsulinism before the appearance of fasting hyperglycemia (1,2). Peripheral insulin resistance plus a pancreatic β-cell insulin secretory defect presumably wage a battle over the years that results ultimately in clinically apparent type II diabetes (3). If this sequence of events is correct, many individuals with type II diabetes have had years of hyperinsulinism, in contrast to their age- and sex-matched control subjects. Further, there may be a disproportionate elevation of plasma proinsulin levels in individuals with IGT and frank diabetes (4,5).

These individuals are at a high risk for cardiovascular events, and this increased risk does not appear to be completely explained by the association of IGT or type II diabetes with such classical risk factors as hypertension, hypercholesterolemia, or cigarette smoking (6). These observations have led to numerous studies directed at determining the pathogenesis of accelerated cardiovascular disease in diabetes; a daunting challenge, for atherosclerosis in nondiabetic individuals is an extraordinarily complex process (7). The early events appear to involve macrophage adherence to endothelium, followed by macrophage migration to the subendothelial space. Here, macrophages may be transformed into foam cells. A variety of growth factors and cytokines may be released from damaged endothelium, macrophages, and smooth muscle cells. Platelets may adhere to the site of macrophage attachment and release thromboxane and growth factors. Smooth muscle cells may proliferate and migrate, accompanied by thrombus formation, vascular encroachment, and occlusion.

In diabetes, added contributors to this process are numerous (8,9). Many investigators have focused on processes that may result from hyperglycemia—an eminently logical (albeit elusive) approach. Provocative findings include subtle endothelial damage, which may accompany increased glucose concentrations in in vitro systems, effects of glycated lipoproteins on macrophage or endothelial function, an increased susceptibility of glycated lipoproteins to oxidation, a litany of effects of oxidized (glycoxidized?) lipoproteins on vascular cell biology, and increased vascular wall levels of irreversible advanced glycation products (8,9). Good evidence suggests that individuals with IGT and hyperinsulinism may have quantitative alterations of plasma lipoproteins that may contribute to accelerated atherosclerosis. Further, a constellation of plasma lipoprotein changes, which theoretically would accelerate atherosclerosis, often are found in people with established type II diabetes, including an increase in plasma triglyceride levels and lowered HDL-cholesterol concentrations (10). The former may reflect increased VLDL production by the liver and/or a decrease in peripheral metabolism, and may be manifested in the ultracentrifuge by a population of small VLDLs and of intermediate-density lipoproteins. These lipoproteins may be particularly atherogenic. Although plasma LDL cholesterol levels may or may not be elevated, evidence is increasing that a family of small, dense LDL particles may be present in diabetes and potentiate atherosclerosis. Such changes also may be found in the insulin-resistance syndrome (syndrome X), which is observed often in individuals with IGT (11).

To complicate matters, individuals with diabetes ap-

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Type II, non-insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; HDL, high-density lipoprotein; VLDL, very-low-density lipoprotein; LDL, low-density lipoprotein; PAI-1, plasminogen activator inhibitor-1; t-PA, tissue-plasminogen activator; type I, insulin-dependent diabetes mellitus; DCCT, Diabetes Control and Complications Trial.

pear to have an increased tendency toward vascular thrombosis. Longitudinal data in individuals with diagnosed type II diabetes indicate that major vascular events such as myocardial infarction and vascular death may occur at a rate of 5–7% per year, even in individuals who have had no known previous cardiovascular event (12). This extraordinarily high cardiovascular event rate is at least three to four times that seen in comparable individuals without diabetes. In addition to clinically recognizable vascular events, individuals with type II diabetes often have unrecognized vascular occlusive disease of the coronary and peripheral vascular systems. The net effect of all of this is an increased recognition by diabetologists, cardiologists, vascular surgeons, epidemiologists, and health professionals in general of the incredible toll that diabetes extracts from the large vessel system.

A hypercoagulable state may exist in diabetes. For instance, subtle alterations of plasma levels of protein C and antithrombin III have been noted and may relate to glycemic regulation with insulin (9). It has long been recognized that the endothelial protein, von Willebrand Factor, may be found in excess in the plasma of diabetic subjects and may relate to the endothelial damage and increased platelet adhesiveness reported in diabetes. An avalanche of studies describes a variety of alterations of platelet function in diabetes (13,14). Clinical trial data in diabetic and nondiabetic subjects indicate that low-dose aspirin therapy to block the platelet release reaction is clearly indicated as a secondary prevention strategy (15). Further, this may prove to be a wise primary prevention approach in the general population (16). A suggestive finding is the elevation of plasma fibrinogen levels in diabetes, particularly in individuals with poor glycemic regulation. A physiological rationale for this finding has been provided by studies that show increased fibrinogen synthesis and turnover in diabetes, related to insulin deficiency and correctable by insulin administration (17,18).

In recent years, attention has been directed to the fibrinolytic system in diabetes, with the expectation that alterations in the balance between fibrin deposition to form a clot and lysis of that clot could help explain thrombotic events in diabetes (19,20,21). The perspective by Schneider et al. (this issue, p. 1–7) is an elegant review of original work from their laboratory and from other researchers who have been active in this rapidly changing field of investigation. Schneider et al., working in an exceptionally strong environment for research in diabetes and its complications at The Washington University School of Medicine, have materially added to our knowledge of the role that alterations of the fibrinolytic system could play in accelerated atherosclerosis and thrombosis in diabetes mellitus. What is important and new about this work? It provides in vitro evidence to support the concept that insulin and proinsulin may accelerate vascular thrombosis via actions on the liver and on the endothelium. Specifically, when exposed to high concentrations of insulin, human hepatoma cells release increased amounts of PAI-1, related to an increase in PAI-1 mRNA expression, probably related to decreased degradation. By using porcine aortic endothelial cells, a good model for atherosclerosis in man, they found that insulin augmented endothelial PAI-1 synthesis, probably by enhancing translation of PAI-1 mRNA. Proinsulin, in concentrations near those that may be observed in type II diabetes, led to an increase in PAI-1 activity, even in the presence of a marked excess of insulin, indicating an insulin-independent pathway. PAI-1 mRNA expression and synthesis were increased concordantly. If these events are operative in vivo, they would support the concept that a diminution in clot lysis, mediated through inhibition of tissue plasminogen activator by PAI-1, may contribute to thrombosis in diabetes.

Other regulators of PAI-1 release have been shown in in vitro systems. Activated macrophages may release cytokines such as tumor necrosis factor and interleukin-1. These cytokines have been shown to suppress t-PA mRNA and to induce transcription of PAI-1 in endothelial cells (23,24). Lipoproteins also may affect this system. Endothelial production of PAI-1 is increased after incubation with VLDL (25), whereas LDL induces PAI-1 synthesis in hepatocytes (26). Thus, critical interrelationships at the site of the atherosclerotic lesions may occur that involve not only insulin and proinsulin but also activated macrophages and altered lipoprotein metabolism in diabetes. Further research is needed in diabetic subjects to continue to unravel the precise sequence of events and involved mechanisms in this very complex system.

What is the clinical implication of this work? Of course, it can be hazardous to transfer in vitro studies to clinical medicine, particularly in a disease as heterogeneous as diabetes mellitus. Nevertheless, the point of view that this system could be of importance is supported by numerous observations. Insulin resistance, coupled with increased plasma immunoreactive insulin levels, may be observed early in the natural history of type II diabetes, and these people appear to be at an increased risk for thrombotic events. Many studies have shown increased plasma PAI-1 levels in people with hyperinsulinism and in type II diabetes (19–21). As noted, plasma proinsulin/insulin ratios may be increased in people with IGT and in those with frank type II diabetes (4,5). Thus, one can visualize a scenario in which hyperinsulinemia and/or hyperproinsulinemia could contribute to vascular thrombosis in type II diabetes via effects on endothelial and/or hepatic PAI-1 synthesis and release.

On the other hand, many unexplained issues remain. As already noted, the pathogenesis of accelerated atherosclerosis in diabetes is incredibly complicated, and it is probably simplistic to speculate that an imbalance in one system, such as the fibrinolytic system, is the major contributor. Further, many conditions are associated with hyperinsulinism, such as obesity, certain forms of type II diabetes, acromegaly, and insulinoma, that do not appear to have accelerated atherosclerosis. Insulin administration to individuals with type II diabetes and marked elevations of fasting plasma glucose (i.e., >11.1 mM [200 mg/dl]) will usually improve the atherogenic lipid profile, protein glycation, and perhaps glycoxidation—processes that, at this stage of diabetes, may be more

critical for accelerating the process of atherosclerosis than is the PA system. Evidence to date does not indicate an effect of insulin on plasma PAI-1 because levels are usually normal in type I patients on insulin (21) and do not rise with acute administration of insulin (19). Indeed, the hypothesis that insulin is atherogenic when administered to diabetic subjects remains controversial (27), and is not supported by available clinical trial data in type II diabetic subjects (28).

Proinsulin may be a very different matter. Many immunoreactive insulin assays apparently cross-react to some degree with insulin. Therefore, studies that show hyperinsulinemia may have been measuring both hormones. Researchers with specific proinsulin assays report an increase in the ratio of proinsulin to insulin in type II diabetes (4,5). Further, proinsulin therapy in one clinical trial was associated with several cardiovascular events, so the trial was stopped. However, increased major vascular events are expected in a type II diabetic population, and unless one follows appropriate control groups simultaneously, one cannot be sure about the specific relationship to proinsulin therapy.

What is the practicing physician who sees diabetic patients to conclude? Should he/she be concerned about the use of insulin for type II patients who have inadequate glycemic control on sulfonylureas? Will this lead to an increase in vascular events? What about insulin use in type I patients? Ongoing studies, such as the DCCT (30) and the UK Prospective Diabetes Trial (31), will give excellent information on the benefits and risks of various forms of therapy in diabetes. However, neither trial is directed at exploring the risks and benefits of the intensive use of insulin in type II patients with hyperglycemia, despite oral agents or standard insulin therapy. Recently, the Department of Veterans Affairs started a feasibility trial of standard insulin therapy versus intensive insulin treatment in such a population (12). It is only through clinical trials of this nature that informed choices can be made by physicians who treat diabetic patients. We urgently need additional studies in other stages of type II diabetes to be able to balance the benefits and risks of various forms of therapy in diabetes as regards cardiovascular disease. Studies such as those by Schneider et al. (this issue, p. 1–7) add important new information to help us understand the pathogenesis of accelerated atherosclerosis and thrombosis in diabetes. From such an understanding, appropriate questions for clinical trials may be asked, and revised standards for clinical care should emerge.

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