Diabetes Mellitus and Vascular Lesions

Daniel Hayoz, Thierry Ziegler, Hans R. Brunner, and Juan Ruiz

Cardiovascular complications represent by far the most severe manifestations of diabetes mellitus. Treatment aimed at stopping progression of vascular lesions may fall short if initiated when the disease becomes clinically evident. Therefore, identification of the earliest vascular disfunctions may offer the best opportunity to interfere with pathogenic mechanisms and avoid progression of diabetic vasculopathy. In this report, we present a few mechanisms that alter hemodynamic and metabolic homeostasis in the course of diabetes mellitus. Endothelial function with special emphasis on nitric oxide and oxidative stress, advanced glycation end products, and the renin angiotensin system are briefly discussed. New pharmacological agents that may favorably influence these parameters are presently undergoing clinical trials. However, tight control of plasma glucose and cardiovascular risk factors represent the cornerstone of the treatment in diabetes to slow progression of vascular disease.

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DIABETES MELLITUS is a multifactorial disease associated with a high risk for vascular complications. The development of vascular disease is only partly preventable by tight glycemic control.[1] Indeed, only a minority of diabetic patients can achieve normoglycemia. Accordingly, late complications of diabetes will still develop in the majority of diabetic patients. Cardiovascular complications represent by far the most common and devastating manifestation and are the major cause of hospital admissions for diabetic patients. In the United States, 77% of hospitalizations of diabetic patients are related to cardiovascular disease and 10% to diabetic nephropathy.[2] The high incidence of cardiovascular disease is not fully explained by hyperglycemia or by an association with other known cardiovascular risk factors. Epidemiologic studies have reported a threefold increase in the relative risk of myocardial infarction compared with matched nondiabetic populations.[3] In patients with claudication of the lower limbs, the presence of diabetes doubles the mortality rate at 5 years to 49% as compared with the 5-year mortality rate of 25% in patients with atherosclerosis without diabetes.[4] The consequences of diabetic microangiopathy and macroangiopathy represent the principal cause of mortality and disability in patients with diabetes mellitus. Although the pathogenetic mechanisms and age distribution differ between type I and type II diabetes, atherosclerosis, retinopathy, nephropathy, and neuropathy develop in both types of diabetic populations at an accelerated rate. Arterial hypertension, which is present in up to 60% of patients with type II diabetes, as well as different forms of dyslipidemia, may amplify or further accelerate the vascular disease that affects most diabetic patients, which explains the higher prevalence of large-vessel lesions in this population.

Is there any evidence that a common functional environment may contribute to diabetic vasculopathy? The pathogenesis of these functional defects in diabetes is not fully understood, and is likely multifactorial with genetically determined susceptibility. Nevertheless, there are a few potentially unifying mechanisms early in the evolution of the disease that merit consideration.

From the Division of Hypertension and Vascular Medicine and Division of Endocrinology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Address reprint requests to Daniel Hayoz, MD, Division of Hypertension and Vascular Medicine, Centre Hospitalier Universitaire Vaudois, 1011 Lausanne, Switzerland.

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0026-0495/98/4712-1005$3.00/0

ENDOTHELIAL FUNCTION

The endothelium plays a key role in maintaining vessel wall homeostasis via the synthesis of several substances that modulate vascular tone, regulate the balance between thrombosis and fibrinolysis, control permeability, and influence smooth muscle cell growth and extracellular matrix composition. It has been shown that endothelial function is already abnormal early in the development of diabetes mellitus. This is now supported both by results obtained in animal models of diabetes mellitus and by functional abnormalities in the coronary and peripheral circulation in patients with type I and type II diabetes.[5-7] Endothelial dysfunction may represent a common pathogenetic framework that contributes in both types of diabetes mellitus to the development of vascular lesions that affect the microcirculation and macrocirculation.

The close association observed between albuminuria and endothelial dysfunction led Deckert et al[8] to postulate the Steno hypothesis, proposing that albuminuria reflects a widespread vasculopathy of the microcirculation and macrocirculation that is the consequence of a generalized endothelial dysfunction.[8]

Several approaches have been used to assess endothelial function in diabetic patients. Among them, the most frequent test applied to quantify endothelial function relies on the rather indirect flow and vessel diameter responsiveness to intra-arterial infusion of muscarinic receptor agonists such as acetylcholine or metacholine. Blunted endothelium-dependent vasodilation in patients with type I and type II diabetes has been reported in the coronary and peripheral circulation in a manner similar to that observed in arterial hypertension, hypercholesterolemia, or postmenopause. However, when flow-mediated vasodilation was assessed following infusion of a potent direct vasodilator distal to the site of arterial diameter measurement (nitroglycerin) or during reactive hyperemia following release of arterial occlusion, no significant changes in vasomotion could be observed between diabetic and control subjects.[6] This is not at all surprising in light of the seminal study by Zeiher et al[9] on the coronary arteries. They showed different sensitivities between the muscarinic agonist infusion and the flow-mediated vasodilation in patients undergoing coronary artery catheterization with differing severity of atherosclerosis. Acetylcholine induced a paradoxical vasoconstriction in angiographically smooth arteries in patients with elevated low-density lipopro-

tein cholesterol. In contrast, flow-mediated vasodilation could still be observed in severely atherosclerotic arteries following distal infusion of papaverine. Although flow-mediated vasomotion represents a more physiologic stimulus to test endothelial function, it has a low sensitivity to identify early endothelial dysfunction in the presence of diabetes or other cardiovascular risk factors.

A series of other indicators have been used to assess endothelial function. Among them, plasma von Willebrand factor (vWF) is an interesting molecule that can be easily assayed without intra-arterial manipulations.[10] However, only patients with type I or type II diabetes and albuminuria were shown to have elevated plasma vWF, suggesting that it reflects marked endothelial cell disruption or activation.[7] New biological indicators of incipient endothelial abnormality are needed to identify patients at risk of developing vascular complications in an attempt to prevent the progression of the disease.

NITRIC OXIDE PATHWAY

What are the mechanisms that may participate in endothelial dysfunction? One possibility is a reduced bioavailability of the endothelium-derived nitric oxide (NO). Different pathways can contribute to the net reduction of bioavailable NO. They include abnormalities in signal transduction, reduced synthesis of NO, enhanced inactivation of NO, and release of competing vasoconstrictors. Supplementation with L-arginine, the substrate for endothelial NO synthase, has a beneficial effect in hypertension and hypercholesterolemia models of endothelial dysfunction, as shown previously. However, in diabetic patients, it does not seem to restore the abnormal vascular response. In a recent study, Nitenberg et al[11] infused coronary arteries of diabetic patients with L-arginine or deferoxamine, a chelator that inhibits reactive oxygen species formation, before challenging the subjects with a cold-pressor test or infusing papaverine. Diabetic patients who exhibited paradoxical vasoconstriction during the cold-pressor test did not show a change in the diameter of the left anterior descending coronary artery (LAD) following L-arginine infusion when challenged again with the cold-pressor test. In contrast, a significant vasodilation of the LAD was observed after infusion of deferoxamine. This supports the observation of Ting et al,[12] who demonstrated a similar effect following intra-arterial infusion of vitamin C in the brachial artery of type II diabetic patients. These findings together suggest that NO inactivation by reactive oxygen species contributes to some extent to the abnormal vasomotion observed in diabetic patients.

ROLE OF ADVANCED GLYCOSYLATION END PRODUCTS AND VASCULAR ENDOTHELIUM GROWTH FACTOR IN ENDOTHELIAL DYSFUNCTION AND VASCULAR PERMEABILITY

Exposure of the vascular environment (proteins and lipids) to increased reducing sugars leads to advanced glycosylation end products (AGEs) and increased oxidative stress that affect the microcirculation and macrocirculation. The formation of AGEs may participate in the process of inactivation of NO. Recent evidence supports the fact that AGEs induce endothelial dysfunction via a receptor-specific pathway (RAGE).[13] The binding of the ligand onto the RAGE induces an increase in permeability that facilitates transmigration of macromolecules through the vessel wall. Prior nonenzymatic glycation and oxidation of the macromolecules favors their trapping in the vessel wall, with a resulting modification of the extracellular matrix composition and the mechanical properties of the vessel wall.

An additional candidate that may favor vascular hyperpermeability in diabetes is vascular endothelium growth factor (VEGF), previously named vascular permeability factor. VEGF is a potent angiogenic factor that also increases vascular permeability. Its implication in vascular growth and permeability in diabetes has been suggested by data showing increased concentrations of VEGF in the ocular fluid of patients with proliferative retinopathy.[14] In an experimental mouse model of proliferative diabetic retinopathy, intraocular injection of a chimeric construct that selectively binds VEGF markedly reduced the proliferative process.[15] Further studies are needed to establish the causality of this factor in the hyperpermeability associated with diabetes. Activation of the fibrinolytic pathway to allow new vessels to make their way into the interstitial tissues represents one of the potential mechanisms by which VEGF may increase permeability.

ROLE OF MECHANICAL FORCES

Using a mechanical model of blood vessels, we are able to reproduce the flow conditions that prevail in the regions prone to the development of atherosclerotic plaque, to study at the molecular and cellular level the mechanisms that may participate in the initiation of the lesion. Cultured endothelial cells grown on compliant elastomer tubings are submitted to different hemodynamic forces, ie, pressure, circumferential stretch, and shear stress.[16] The typical flow environment encountered in the plaque-prone regions, represented by the flow dividers and curvatures, is characterized by an oscillatory flow with a negligible mean shear stress. Under such simulated high-risk conditions, we can demonstrate a reduction of the constitutive endothelial NO synthase mRNA expression compared with cells submitted to normal flow conditions, ie, pulsatile flow with a high mean shear stress and no reverse flow. Most interestingly, concomitant with the reduction in NO synthase mRNA expression, we can show an induction of VEGF mRNA expression (Fig 1). Thus, VEGF may represent an additional factor favoring increased permeability of the vessel wall in a region prone to plaque development. These deleterious conditions (ie, reduced NO availability and increased permeability) may concentrate at sites along the vascular tree predetermined by flow patterns where altered macromolecules and circulating monocytes have facilitated access to the subendothelium because of increased residency time.

ROLE OF THE RENIN-ANGIOTENSIN SYSTEM

To further underline the potential importance of this concept of increased oxidative stress and hyperpermeability, one should also discuss the role of the renin-angiotensin system (RAS). As mentioned earlier, the prevalence of hypertension is high in type II diabetes, whereas it is not significantly different in type I diabetes before nephropathy becomes evident. The efficacy of angiotensin-converting enzyme (ACE) inhibitors in the treatment of hypertensive diabetics is well established. More recently, the observation that ACE inhibitors can prevent or

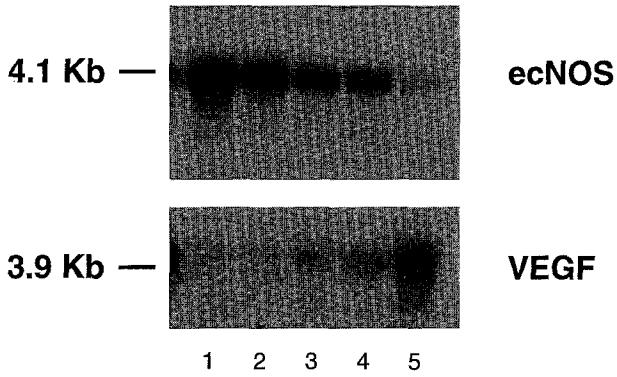

Fig 1. Northern blot analysis of total mRNA obtained from bovine aortic endothelial cells exposed to different combinations of mechanical stress for 24 hours hybridized with a bovine cDNA probe for ecNOS (top) and VEGF (bottom). Lane 1, combination of pressure (100 mm Hg), shear stress of 6 dyn/cm², and circumferential stretch of 4%; lane 2, combination of pressure and shear stress of 6 dyn/cm²; lane 3, combination of pressure and shear stress of 0.3 dyn/cm²; lane 4, combination of pressure, shear stress of 0.3 dyn/cm², and circumferential stretch of 4%; lane 5, static control.

retard the progression of nephropathy in both hypertensive and normotensive patients with type I diabetes represents a landmark result.[17] It is very likely, from the available published data, that ACE inhibitors have a unique capacity independent of their antihypertensive or hemodynamic effects to slow the progression of diabetic vasculopathy in type I and type II diabetes.

The RAS may play a role in the NO/reactive oxygen species balance, as angiotensin II (AII) has been directly implicated in the generation of superoxide anion in smooth muscle cells. Indeed, AII regulates a membrane-bound flavin containing NADH/NADPH oxidase that produces oxygen radicals.[18] Several groups have reported that AII increases the net production of superoxide anion in cell culture and in animal models of hypertension. One could then hypothesize that ACE inhibitors, besides their well-known hemodynamic action, could participate in the reduction of oxidative stress in the vessel wall. Such a concept, before discovering this interesting enzymatic oxidase induction, was discussed a few years ago when normotensive hypercholesterolemic rabbits treated long-term with ACE inhibitors showed a dramatic reduction of plaque formation.[19] Similar results were subsequently obtained in a normotensive hypercholesterolemic pig model.[20]

Clinical studies and trials have confirmed the ability of ACE inhibitors to restore endothelial function in hypertensive patients and in normotensive subjects with other pathologic cardiovascular conditions.[21,22] This accessory property of ACE inhibitors via a redox-sensitive mechanism would definitely represent a welcome asset by reducing the proinflammatory consequences of an excess of reactive oxygen species.

As discussed earlier, the vascular hyperpermeability present in diabetic patients may be the direct consequence of an increased amount of AGEs that react with their receptor on the endothelium. Blockade of the RAGE with an antibody considerably reduced the permeability of the vessel wall, but did not totally abolish it. One of the possible candidates that may influence the tightness of the endothelial barrier, as mentioned earlier, is VEGF. Interestingly, Williams et al[23] recently reported that AII upregulates the expression of VEGF mRNA expression, which can also be markedly increased in the presence of an elevated glucose concentration (20 mmol/L). Blockade of the AT1 receptor with losartan abolishes the expression of VEGF mRNA.

Thus, the vasoprotective effect of ACE inhibitors does not appear to be restricted to their hemodynamic properties. Modulation of cytokines, growth factors, and reactive oxygen species production most likely contributes to the beneficial renal and vascular effects demonstrated in clinical trials in diabetic patients. Increased oxidant stress is emerging as a potential key culprit in the development of atherosclerosis, hyperpermeability, and sclerosis of arterial blood vessels. An approach aimed at improving redox-sensitive mechanisms and reducing cytokine and growth factor release has the potential to prevent or delay atheromatous vascular complications in diabetes. The precise clinical benefit that can be derived from this approach, as well as the timing and duration of the inhibition needed, remains to be further clarified.

Taken together, cardiovascular complications in diabetic patients clearly have a multifactorial origin. Among the many mechanisms contributing to development of the lesions are impaired endothelial function possibly related to enhanced NO turnover, AGEs, and increased oxidative stress, altered mechanical forces on the arterial wall, as well as AII. For the moment, inhibition of AII synthesis by ACE inhibition provides a new therapeutic approach to the treatment and prevention of vascular lesions in diabetic patients.

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