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The Pathologic Continuum of Diabetic Vascular Disease

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Hyperglycemia can promote vascular complications by multiple mechanisms, with formation of advanced glycation end products and increased oxidative stress proposed to contribute to both macrovascular and microvascular complications. Many of the earliest pathologic responses to hyperglycemia are manifest in the vascular cells that directly encounter elevated blood glucose levels. In the macrovasculature, these include endothelial cells and vascular smooth muscle cells. In the microvasculature, these include endothelial cells, pericytes (in retinopathy), and podocytes (in renal disease). Additionally, neovascularization arising from the vasa vasorum may promote atherosclerotic plaque progression and contribute to plaque rupture, thereby interconnecting macroangiopathy and microangiopathy. (J Am Coll Cardiol 2009;53:S35–42) © 2009 by the American College of Cardiology Foundation

Type 2 diabetes mellitus (T2DM) is diagnosed, and hence largely defined, by hyperglycemia. Although this definition has framed the perspective on T2DM, the pathologic imprint of this disease often involves the vasculature, with the hyperglycemia promoting both microvascular and macrovascular complications. Not surprisingly, given complications such as stroke and acute coronary syndromes, much attention has focused on diabetic macrovascular disease. However, the morbidity associated with diabetic microvascular disease, including retinopathy, neuropathy, nephropathy, and limb ischemia, is staggering. Given the impact of diabetic vascular disease, prodigious effort has been directed toward improving vascular outcomes in T2DM. Improving macrovascular outcomes through glucose-lowering interventions has remained a difficult, complicated, and to date, largely unsuccessful enterprise. In contrast, tighter glucose control does limit microvascular disease. These seemingly paradoxical trends force re-examination of the diabetic vascular disease spectrum.

Diabetic Macrovascular Complications

Hyperglycemia can promote vascular complications by multiple postulated mechanisms (Table 1). Increased glucose concentrations can activate nuclear factor-κB (1), a key mediator that regulates multiple pro-inflammatory and pro-atherosclerotic target genes in endothelial cells (ECs), vascular smooth muscle cells (VSMCs), and macrophages. Elevated glucose can foster glycation of proteins, promoting formation of advanced glycation end products (AGEs) protein cross-linking, and reactive oxygen species formation. Hyperglycemia itself can stimulate oxidative stress, which has been strongly implicated as a driving force in atherosclerosis.

Not surprisingly, many early pathologic responses to glucose are manifest in the vascular cells that directly encounter hyperglycemia. The loss of the nonadhesive property of the endothelium, with monocyte adhesion to ECs, is an early atherogenic step. Hyperglycemia increases monocyte adhesion to cultured ECs (2). Hyperglycemia and AGEs can also stimulate EC production of superoxide (1,3), suggesting links between hyperglycemia, AGEs, and oxidative stress. Glucose may also activate matrix-degrading metalloproteinases, enzymes implicated in plaque rupture and arterial remodeling, inducing similar responses in VSMC. Glucose may also stimulate VSMC proliferation, migration, and altered reactivity, for example, through renin-angiotensin activation.

Inflammation has been strongly implicated in both atherosclerosis and T2DM (4–6). Despite this, no single mechanism yet explains why this pattern is found in diabetic patients. Monocytes grown in the presence of high glucose concentrations or isolated from persons with poorly controlled diabetes appear activated (7), with induction of many inflammatory mediators such as protein kinase C and nuclear factor-κB. These targets, as well as others, may promote oxidative stress (8). In vitro studies suggest similar pro-atherogenic effects of hyperglycemia on T lymphocytes, inflammatory cells also involved in atherosclerosis.

Hyperglycemia Versus Dyslipidemia in the Pathogenesis of Atherosclerosis

Attempts to improve cardiovascular (CV) outcomes through glucose control contrast strikingly with the benefits seen in

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Abbreviations and Acronyms

AGE = advanced glycation end product
APC = activated protein C
CV = cardiovascular
EC = endothelial cell
ER = endoplasmic reticulum
PEDF = pigment epithelium-derived factor
PPAR = peroxisome proliferator-activated receptor
T2DM = type 2 diabetes mellitus
VEGF = vascular endothelial growth factor
VSMC = vascular smooth muscle cell

most trials with statins in patients with diabetes. Such data challenge the focus on glucose as the prime determinant of pathologic, or at least vascular, outcomes among patients with diabetes. The relative effects of hyperglycemia versus dyslipidemia in atherogenesis have been difficult to separate. For example, dyslipidemia can be exacerbated by hyperglycemia. At the same time, some data suggest possible independent effects of hyperglycemia on atherosclerosis (9,10). Atherosclerosis was found to develop more rapidly in fat-fed diabetic pigs than in similar dyslipidemic fat-fed pigs without diabetes (9). In low-density lipoprotein receptor-deficient mice with a novel form of diabetes induced by a T-cell–directed viral antigen, consumption of a cholesterol-free diet resulted in hyperglycemia without changes in lipids or lipoproteins (10). Adding increasing amounts of dietary cholesterol led to dyslipidemia, which was the major factor in atherosclerosis progression independent of hyperglycemia in this model (10).

Endoplasmic reticulum (ER) stress may promote atherosclerosis among those with diabetes. All secretory and membrane proteins, many pathogens, and diverse nutrients, including glucose, pass through the ER. Hyperglycemia alone can induce ER stress in multiple tissues, including the liver and fat, activating pathways involved in oxidation and inflammation (11). Thus, ER stress, which can also be stimulated by hypoxia, elevated free fatty acids, and other nonglucose pathways, may promote both diabetes and atherosclerosis (12).

It is of interest to overlay these various postulated mechanisms that promote inflammation and macrovascular disease onto microvascular disease. As noted, in contrast to macrovascular disease, the impact of better glycemic control on microvascular disease is unequivocal. This divergence in clinical experience raises fundamental questions about the nature of microvascular disease, how hyperglycemia modifies the microvasculature, and the implications of differing glucose effects on arterial disease, based on vessel size.

Diabetic Microvascular Complications

Pathological changes in the diabetic microvasculature can alter organ perfusion, particularly affecting organs heavily dependent on their microvasculature supply, namely the retina, kidneys, and peripheral nervous system. The clinical problems associated with these changes—retinopathy, nephropathy, and neuropathy—drive a large burden of T2DM morbidity. Microvascular disease also contributes to peripheral vascular disease, reduced myocardium vascularization, and poor wound healing (13). To some extent, diabetic microvascular disease has been overlooked in terms of its clinical impact and research attention. Further consideration of microvascular disease should begin with an overview of the anatomic nature of the microvasculature.

Structural and Functional Differences: Micro Versus Macro

Microvessels—the smallest functional unit of the CV system—consist of arterioles, capillaries, and venules. These vessels differ significantly from macrovessels with respect to architecture and cellular components. In contrast to larger vessels providing blood to organs, microvessels have specific roles regulating blood pressure and offering nutrient delivery. The microcirculation also has regulatory systems such as vasomotion, permeability, and myogenic responses that can adapt flow to local metabolic needs (14,15). Disturbances in microvascular function may arise before overt hyperglycemia

Table 1 Examples of Mechanisms Implicated in Diabetic Macrovascular Disease

Cellular Players	Mechanisms
Endothelium	NF-κB activation
	Decreased NO production
	Increased reactive oxygen species
	Increased harmful metabolites (peroxynitrite, nitrotyrosine)
	Increased lipid peroxidation products
	Impaired endothelial-dependent relaxation
Monocyte-derived macrophages	Increased IL1β, IL6, CD36, MCP-1
	Induction of protein kinase C
Vascular smooth muscle cells	Increased proliferation
	Increased migration into intima
	Altered matrix components (chondroitin, dermatan sulphate proteoglycans)
	Increased matrix degradation (elastin)
	Increased nonenzymatic collagen glycation

AGE = advanced glycation end products; IL = interleukin; MCP = monocyte chemoattractant protein; NF-κB = nuclear factor-kappa B; NO = nitric oxide.