Type 2 Diabetes Is More Than Hyperglycemia

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According to *Webster's II New College Dictionary*, type 2 diabetes mellitus is defined as a ". . . form of diabetes mellitus that typically appears first in adulthood and is exacerbated by obesity and an inactive lifestyle . . . [and] is usually diagnosed by tests that indicate glucose intolerance. . . ."[1] *Merriam-Webster's Medical Desk Dictionary* defines type 2 diabetes mellitus as "a common form of diabetes mellitus that develops especially in adults and . . . in obese individuals and that is characterized by hyperglycemia resulting from impaired insulin utilization coupled with the body's inability to compensate with increased insulin production."[2]

All true. But these definitions fail to identify that hyperglycemia is only one part of the picture. Patients with type 2 diabetes typically have a constellation of associated conditions—abnormal lipid metabolism, hypertension, and abdominal obesity—in addition to disordered glucose metabolism. This constellation of conditions is now considered a metabolic syndrome that confers increased risk for the development of macrovascular complications, in particular, cardiovascular disease (CVD).

A wealth of clinical evidence has demonstrated that treating lipid disorders and hypertension reduces CVD risk. While much epidemiological evidence has linked hyperglycemia and CVD even at glycemic levels that fall

below the diabetic range, clear evidence that treatment of hyperglycemia per se will reduce CVD is lacking.

Still, there are many logical reasons to believe that controlling hyperglycemia would reduce macrovascular damage. A myriad of physiological effects of chronic hyperglycemia are not healthy for blood vessels, including excessive production of advanced glycation end products, activation of protein kinase C isoforms, and sorbitol accumulation.[3] All of these may be atherogenic through a variety of mechanisms. One such mechanism is the stimulation of cytokines, which mediate vascular injury both through direct toxic effects and indirectly, for example, by increasing plasminogen activator inhibitor type 1 activity and C-reactive protein production.[4]

Despite a lack of hard evidence indicating a relationship between treatment of hyperglycemia and reduction in CVD, type 2 diabetic patients and their health care providers tend to focus on glycemic control as paramount. Sixty-five percent of primary care physicians in an American Diabetes Association poll believed that glycemic control was more effective than blood pressure or lipid control in preventing CVD.[5]

Certainly, there are reasons to be aggressive about the treatment of hyperglycemia. Evidence from studies such as the Diabetes Control and Complications Trial and the U.K. Prospective Diabetes Study, which showed that improved glycemic control can prevent the onset or progression of microvascular complications, has made us aim at lower blood glucose targets. But patients with diabetes die from CVD, which is the result of the interaction of a number of different hemodynamic and metabolic factors. And while I, personally, believe that glycemic control is one of them, definitive evidence is needed. I refer readers to the feature article by Carlos Abraira, MD, and William Duckworth, MD, in this issue (p. 107) for a discussion of this subject.

Results from studies such as the Veterans Affairs Diabetes Trial[6] and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[7] may or may not demonstrate that better treatment of hyperglycemia in people with diabetes lowers CVD risk. But regardless of those results, it still will be necessary to aggressively treat all of the other so commonly associated features of diabetes—lipids, blood pressure, and obesity—to effectively reduce the risk of CVD in our patients. Type 2 diabetes—and CVD—are more than just hyperglycemia.

REFERENCES

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[6]Abraira C, Duckworth W, McCarren M, Emauele N, Arca D, Reda D, Henderson W, for the participants of the VA Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type 2: Design of the cooperative study on glycemic control and complications in diabetes mellitus type 2 Veterans Affairs Diabetes Trial. *J Diabetes Complications* 17(4), July 2003. In press

[7]Action to Control Cardiovascular Risk in Diabetes (ACCORD), sponsored by the National Heart, Lung and Blood Institute. www.clinicaltrials.gov