Endothelial Vasodilation Effects of Statins in Type 2 Diabetic Patients

Response to van Venrooij et al.

In this issue of Diabetes Care, there is an intriguing report of a double-blind, placebo-controlled, randomized study demonstrating that lipid-lowering treatment for 3 weeks with the powerful hydroxymethylglutaryl (HMG)-CoA reductase inhibitor (statin) atorvastatin did not reverse endothelial-dependent and -independent vascular dysfunction in 133 patients with type 2 diabetes (mean disease duration 11.5 years) and dyslipidemia (1). This observation is in stark contrast to results in nondiabetic dyslipidemic patients and insulin-resistant nondiabetic subjects in which HMG-CoA reductase therapy improved endothelium-dependent vascular relaxation (2–5). However, the study by van Venrooij et al. (1) is in agreement with a prior smaller study that observed no improvement in endothelial-derived vasodilation after statin treatment of established type 2 diabetic patients (6). This raises the vexing question as to why these agents do not have the same effects on vascular function in established type 2 diabetic patients as in patients with dyslipidemia or insulin resistance or in those at risk or in the early stages of diabetes.

Statins appear to have direct cardiovascular disease (CVD) protective effects. For example, in the WOSCOPS (West of Scotland Coronary Prevention Study) (7), the time-to-event curves began to diverge within 6 months of initiation of therapy, an effect that is earlier than predicted from cholesterol lowering alone. Clinical trials have also demonstrated greater CVD benefits than that predicted by minimal changes in luminal dimensions on angiography, benefits that cannot be explained by simple plaque regression (5). A major potential mechanism that may mediate some of these beneficial effects includes improvement in vascular endothelial function (5). Basal and stimulated endothelium-dependent forearm blood-flow responses improve in hypercholesterolemic patients after 1 month of statin therapy (4). Statins increase endothelial nitric oxide (NO) production and improve NO-dependent vasorelaxation in different vascular beds (5). Statins up-regulate endothelial NO synthase (eNOS) (8) and the inducible form of NOS (iNOS) (9) in vascular smooth muscle cells, with both processes augmenting vascular blood flow. Statins also appear to reduce the oxidative destruction of NO (5), a process that is enhanced in subjects with insulin resistance and diabetes (10). Indeed, endothelial dysfunction is a hallmark of diabetes and insulin-resistant states and is characterized by reduced effective vascular NO action (10).

Why does statin therapy not improve NO-mediated vasodilation in patients with established diabetes and dyslipidemia (1,6)? The answer likely relates to structural and morphological changes in patients with well-established diabetes (11) as opposed to reversible endothelial dysfunction, which precedes these structural changes in subjects with insulin resistance and the early stages of diabetes (10). A major factor in these more permanent structural changes in established diabetes is the formation of advanced glycation end products (AGEs) through a complex series of rearrangements between reducing sugars and free amino groups (12–15). AGEs reduce biologically active NO, increase extracellular matrix, enhance coagulation, and attenuate endothelial-derived vasorelaxation (12–15). The accumulation of AGEs on long-lived matrix proteins increases the cross-linking of these components, resulting in their resistance to degradation as well as increasing vessel rigidity and the possibility of atherosclerosis (12–15). These vascular changes are associated with both availability of NO and response to NO (15), perhaps explaining the lack of improvement in endothelial-derived vasodilation and vasodilatory responses to nitroglycerine after statin therapy in patients with established diabetes and dyslipidemia.

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References