Cerivastatin and Endothelial Function in Elderly Patients With Diabetes Mellitus

To the Editor:

In the recent article by Tsunekawa et al.,1 3 days of therapy with the HMG Co-A reductase inhibitor cerivastatin improved flow-mediated vasodilation (FMD) of the brachial artery in a cohort of 27 older patients with diabetes mellitus (mean age 69.3±3.4 years). We found the results of this investigation puzzling for two reasons.

First, we were surprised by the magnitude of the benefit of statin therapy, which in this study led to nearly a doubling in FMD and an absolute increase of approximately 4% after 3 days of therapy. The magnitude of the improvement in FMD is much higher than previously reported in larger studies with other statins using similar techniques over longer periods of time.2,3

We have demonstrated that two other statins, alone and in combination with antioxidant vitamins, did not improve brachial artery FMD after 1 year of therapy in twice as many older adults (≥70 years old).4 The magnitude of the improvement in FMD and its variance from previous studies needs to be addressed by the authors.

We were also surprised that FMD of the brachial artery exceeded nitroglycerin-mediated vasodilation in this trial. Because nitroglycerin is an endothelium-independent vasodilator, it typically leads to more vasodilation than does flow, which is an endothelium-dependent vasodilator. In our review of over 150 published manuscripts, we have never found a study where FMD was greater than nitroglycerin-mediated vasodilation. Furthermore, the amount of nitroglycerin-mediated vasodilation in the present study was much lower than in previous studies,2−3 including those of similar-aged subjects.4,5

It is possible that the baseline brachial artery diameters varied between conditions in this study, which may have accounted for apparent changes in FMD. This information was not provided by the authors. Although we applaud their efforts to gain insight into non-lipid-mediated effects of statins and their interest in geriatric preventive cardiology, these issues should be discussed in more detail.

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Response

We are grateful to Drs Stein and Carlson for their interest in our article.1 We were also surprised by the drastic change of flow mediated vasodilatation (FMD) after statin therapy. However, the adequacy of the results was supported by the increase of both plasma NO2−/NO3− and cGMP concentration. Moreover, a decrease of plasma 8 isoprostane, an oxidant marker, may increase NO bioavailability. We cannot discuss the reason of the discrepancy between our data and theirs, because their report has not yet been published. However, the hypercholesterolemia in their subjects is itself known to impair FMD. Our previous data regarding a rabbit model showed that impaired endothelium-dependent relaxation in hypercholesterolemia-induced atherosclerosis could not be restored easily.2 For that reason, we selected subjects without severe hypercholesterolemia (total cholesterol 200 to 260 mg/dL). The impairment of endothelium-dependent relaxation in diabetes mellitus is suggested not to be severe, and scavenging oxygen radicals could restore it. Moreover, the difference in non−lipid-mediated effects between statins should be considered, because cerivastatin has the strongest bioavailability among statins currently accessible. Recently, cerivastatin was reported to have a stronger pleiotropic effect than atorvastatin.3

Their second question is in regard to the fact that FMD exceeded nitroglycerin−induced endothelium independent dilatation (NTG−D) after statin therapy. We suggest the lack of validity of comparing FMD and NTG−D using this method. Because the conditions of the two measurements are completely different (ie, reactive hyperemia and sublingual perfusion of nitroglycerin), and both values were decided at only one point (5 minutes prevention of blood flow in measuring FMD and 300 μg nitroglycerin infusion in measuring NTG−D). In comparing the endothelium−dependent ability of smooth muscle cell relaxation with that of the endothelium−independent ability, the same mode of drug administration or stimulus to induce vascular response should be applied. It may be useful to examine the cumulative concentration of acetylcholine and nitroglycerin infusion into the brachial artery.4 Moreover, we should be aware of each patient’s profile, because NTG−D is reduced in elderly diabetic patients.

Both endothelium−dependent and endothelium−independent relaxations are impaired in diabetic patients.5 In our previous study, diabetes and aging synergistically impaired endothelium−independent relaxation. The possible effect of aging in drug absorption by sublingual infusion of NTG also has to be considered. Certainly, a non−invasive technique using sonography is insightful; however, we are aware of the limitations of this methodology for interpreting the results. Although we applaud their interest in geriatrics, we must comment that the question raised is neither essential nor relevant because of the reasons described above.

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