Distinct Metabolic Effects of Different Classes of Antihypertensive Drugs

To the Editor:

Eriksson et al.1 investigated insulin action and secretion and body fat distribution after treatment with candesartan, hydrochlorothiazide, and placebo in 22 hypertensive patients. They found that blood pressure was reduced similarly by candesartan and hydrochlorothiazide versus placebo after a 12-week treatment period. Nonetheless, visceral fat redistribution, liver fat accumulation, low-grade inflammation, and aggravated insulin resistance were demonstrated after hydrochlorothiazide but not candesartan treatment.

Recent meta-analyses have demonstrated that, among antihypertensive drugs, β-blocking agents and thiazide diuretics have been reported to impair insulin sensitivity and to potentially increase the risk for type 2 diabetes mellitus, and inhibition of the renin-angiotensin system with angiotensin-converting enzyme inhibitors or blockers of the type 1 angiotensin II receptor is beneficial.2

Distinct metabolic effects of different classes of antihypertensive drugs may be the result of several interacting mechanisms that target the vicious synergy between endothelial dysfunction and insulin resistance. We investigated metabolic effects of either placebo or one class of antihypertensive drug (atenolol 100 mg, amlodipine 10 mg, hydrochlorothiazide 50 mg, ramipril 10 mg, or candesartan 16 mg) in 31 hypertensive patients during 8 weeks in each of 6 arms of a randomized, single-blind, placebo-controlled, parallel study.3 All of the antihypertensive drugs significantly reduced blood pressure when compared with placebo. Atenolol and thiazide therapies increased triglyceride levels greater than ramipril or candesartan (P<0.005 by ANOVA). Ramipril and candesartan therapies improved flow-mediated dilation and increased adiponectin levels and insulin sensitivity to a greater extent than atenolol or thiazide therapies (P<0.001 and P<0.015 by ANOVA). Ramipril, candesartan, and amlodipine therapies significantly decreased leptin levels to a greater extent when compared with atenolol or thiazide therapies (P<0.001 by ANOVA). We observed differential effects of antihypertensive drugs on endothelial dysfunction and plasma adipocytokines.

Angiotensin II increases leptin secretion from cultured human fat cells. Leptin may potentiate pressor effects of hyperinsulinemia in insulin-resistant states. Therefore, interactions between angiotensin II and insulin may have deleterious cardiovascular effects in obesity. In addition, leptin appears to stimulate vascular inflammation, oxidative stress, and vascular smooth muscle hypertrophy. These actions may contribute to the pathogenesis of hypertension, atherosclerosis, and left ventricular hypertrophy.4 Inhibition of the renin-angiotensin system abolishes the effect of angiotensin II to promote leptin production.

Based on solid evidence from both translational basic science and clinical intervention trials, there is emerging support for simultaneously targeting multiple therapeutic pathways in the optimal treatment of hypertension. Thus, these studies suggest that the particular therapeutic strategy used to target blood pressure may be an additional important factor to consider in addition to simply monitoring improvement in a biomarker, perhaps.5 Design of future clinical trials should take into account comparison of therapeutic strategies in addition to simple comparisons of biomarkers.6,7

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Disclosures

None.

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