Comment on: Song et al. (2009) Effect of Homocysteine-Lowering Treatment With Folic Acid and B Vitamins on Risk of Type 2 Diabetes in Women

A Randomized, Controlled Trial. Diabetes 58:1921–1928

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The *Diabetes* article by Song et al. (1) presents the results of the first randomized, controlled trial to analyze the long-term effects of folic acid and vitamin B supplementation on the risk of developing type 2 diabetes in women at high risk for cardiovascular disease. Daily supplements significantly lowered homocysteine levels but did not reduce the risk of developing type 2 diabetes. Their results do not support previous findings indicating increased homocysteine levels as a significant predictor of the development of diabetes (2).

These conflicting data must be viewed in light of the increasing evidence gained from clinical trials, which suggests no beneficial effects of homocysteine-lowering strategies on cardiovascular events (3). Given the controversy, it has been suggested that *S*-adenosylhomocysteine (SAH), the cytotoxic precursor of homocysteine, may be a more sensitive indicator of cardiovascular disease than is homocysteine (4). We have recently studied the mechanisms by which homocysteine and SAH cause endothelial cell damage (5). In our study, human coronary artery endothelial cells were unaffected by exposure to homocysteine, even at supraphysiologic concentrations (500 μmol/l); however, low concentrations (25 μmol/l) of homocysteine induced cytotoxic changes in endothelial cells under culture conditions that increased the intracellular level of SAH (5). We believe our findings show that in the absence of SAH, the vascular effects of homocysteine may be negligible.

These findings may help explain the lack of health benefits observed in several nutritional intervention trials, including that of Song et al. (1). Vitamin supplements that successfully lower homocysteine levels may not affect SAH levels. It would be of interest to see a large-scale, prospective study of SAH, rather than homocysteine, as an indicator of the development of diabetes.

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