Homocysteine and Cholesterol: Guilt by Association?

To the Editor:

Since the start of folate fortification in the United States, there has been a long debate about whether B vitamins might protect from age-associated diseases. Because hyperhomocysteinemia (HHCY) in stroke patients is very impressive, numerous studies anticipated a beneficial effect of tHcy-lowering.

A report from the HOPE-2 study documented that daily supplement of folic acid, vitamin B6, and B12 for 5 years reduced the risk of stroke by 25%. The beneficial effect of the vitamins was larger in subjects with certain risk profile or medications, and no marked effect can be expected in the first 3 years of supplementation. Patients receiving antiplatelet agent or cholesterol-lowering drugs or those coming from a country with folate fortification were less likely to benefit.1

The HOPE-2 study clearly showed that several confounding factors were underestimated in similar studies. If cholesterol-lowering will lower the awaited effect of tHcy-lowering, the power calculation of numerous large trials must be reconsidered. Because the protective effect of tHcy-lowering was more impressive in the group with high tHcy and cholesterol, this suggests that HHCY can accelerate atherosclerosis when associated with elevated plasma lipids.

The SEARCH study is another large randomized trial for the effect of intensive cholesterol-lowering-treatment (80 mg versus 20 mg simvastatin) on the vascular, cerebral or noncoronary events. In a 2×2 factorial design, participants were randomized to receive folate and B12 or placebo for approximately 6.7 years.2 The current report of the HOPE-2 study strongly suggests that the design of SEARCH study is not appropriate to detect an independent effect for the vitamins on the vascular risk. The study should consider the interactive effect of tHcy-lowering therapy and statins.

Hyperhomocysteinemia and dyslipidemia are associated. In the Hordaland study, the intake of saturated fatty acids was positively associated with plasma tHcy.3 Statins lower the risk for future cardiovascular disease and stroke4 and also lower plasma tHcy. Additionally, a negative association between tHcy and HDL cholesterol has been reported.5 Low HDL cholesterol is a risk factor for atherosclerosis and a component of diabetes mellitus and the metabolic syndrome. Diabetes mellitus is a common soil for HHCY and hypercholesterolemia and a factor that impacts the effect of tHcy-lowering on vascular disease.

In contrast to statins, the benefit of treatment with fenofibrate6 might be counterbalanced by a sustained increase in plasma tHcy. One might assume that the endothelial system that is prone to accumulate lipids might be extremely sensitive to HHCY. We anticipate that a combined cholesterol- and tHcy-lowering drugs for patients with multiple risk factors might be more effective than each of them.

Finally, the beneficial effect of tHcy-lowering seems to be more impressive in stroke compared to coronary events lending more support to the Hcy hypothesis. Because elderly people with multiple risk factors might equally develop either cardiovascular disease or stroke, physicians should realize that if vitamin B supplementation can protect against stroke, it should be recommended for all population regardless of the effectiveness of this treatment on cardiovascular disease.

Disclosures

None.

Rima Obeid, PhD
Wolfgang Herrmann, PhD
Department of Clinical Chemistry and Laboratory Medicine
University Hospital of the Saarland
Homburg, Germany


(Stroke. 2009;40:e516.)

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Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.109.551416 e516
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Stroke. 2009;40:e516; originally published online May 21, 2009;
doi: 10.1161/STROKEAHA.109.551416

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