Letters to the Editor

Mild hyperhomocysteinemia: vitamin supplementation or not?

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Dear Sir:

We read with interest the articles by Brattström and Wilcken (1) and Ueland et al (2), which raise several important questions about homocysteine and cardiovascular risk.

We studied 62 adults aged <45 y with vascular disease [20 with cerebrovascular disease (stroke or TIA; group 1), 20 with deep-vein thrombosis (group 2), and 22 with retinal vein occlusion (group 3)] and 25 healthy control subjects (3–6). We measured glucose, total cholesterol, triacylglycerol, creatinine, red blood cell folate, serum vitamin B-12, and plasma total homocysteine (tHcy) concentrations in blood samples collected at 0 h. An additional blood sample for measurement of plasma tHcy was collected 4 h after administration of oral methionine (100 mg L-methionine/g diluted in orange juice).

tHcy was determined by HPLC with fluorescence detection. In all patients, we tested for a mutation in the coding region of the *MTHFR* gene—a C-to-T substitution at nucleotide 677 (*MTHFR* 677C→T); 9.5% and 9.8% of groups 1 and 2, respectively, were homozygous for the *MTHFR* 677C→T polymorphism (NS compared with the control group). In group 3, 18% of the patients were homozygous for the mutation, which was significantly different from the value (10%) in control subjects ($P < 0.05$).

tHcy concentrations before and after the methionine load were higher in 15% of the patients in groups 1 and 2 than in the control subjects (fasting values: 12.5 ± 6.5 μmol/L compared with 7.6 ± 4.1 μmol/L; after the methionine load: 28 ± 10.1 compared with 17.4 ± 6.5 μmol/L); there was no significant increase in group 3. Values ≥12 μmol/L were considered to indicate fasting hyperhomocysteinemia.

Our studies raised 2 questions: *1*) Should we treat patients with mild hyperhomocysteinemia but not homozygous for the *MTHFR* 677C→T polymorphism or patients homozygous for the mutation but with normal tHcy concentrations? *2*) Should decisions about treating mild hyperhomocysteinemia be based on absolute tHcy concentrations or on differences between tHcy concentrations measured after fasting and those measured after a methionine load?

Because homozygosity for the *MTHFR* 677C→T mutation is expected to increase cardiovascular risk only when tHcy concentrations are mildly elevated, we suggest that only patients with mild hyperhomocysteinemia receive folate supplementation. Finally, we believe that other risk factors that may provoke vascular lesions in patients with mild hyperhomocysteinemia must be considered before any decisions regarding folate supplementation be made.

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Reply to R Cerone et al

Dear Sir:

We thank Cerone et al for their comments about our article. In relation to the 2 questions they posed, the first relates to the question of whether to treat patients with mild hyperhomocysteinemia but no 677C→T mutation (C-to-T substitution at nucleotide 677) of the *MTHFR* gene or patients homozygous for the mutation but with normal total homocysteine concentrations. We attempted to answer this question in a meta-analysis of 23 case-control studies involving 5869 patients with established atherosclerotic vascular disease and in 6644