Effects of folic acid on homocysteine in persons classified by methylenetetrahydrofolate reductase genotype

Dear Sir:

Woodside et al (1) recently published an interesting study of the effects of folic acid and vitamins B-6 and B-12 on total plasma homocysteine (tHcy) concentrations in 132 men stratified for the common heat-labile polymorphism [a C-to-T substitution at nucleotide 677 (C677T)] in the gene for methylenetetrahydrofolate reductase (MTHFR). On the basis of results from a subgroup of 50 subjects in this study, the authors concluded that persons who are homozygous (T/T) for the polymorphism are less responsive to the effects of folic acid and B-vitamin supplementation than persons homozygous for the nonthermolabile allele (C/C). They also hypothesized that doses of folic acid > 1 mg/d may be required to reduce plasma tHcy concentrations in the T/T subgroup.

These results are in contrast with those from our previous studies of the effects of supplementation with 1 or 2 mg folic acid/d in 242 men and women classified by coronary artery disease status, multivitamin use, and the C677T MTHFR genotype (2). The results of our study, and those of studies by Jacques et al (3) and Deloughery et al (4), suggest that T/T homozygotes are more sensitive to the adverse tHcy-raising effects of reduced plasma folate concentrations. Moreover, our T/T subjects experienced much greater decreases in plasma tHcy concentrations after receiving 1 or 2 mg folic acid/d for 3 wk than did C/C subjects (2). Among subjects who were not previously taking multivitamins, the mean reductions in plasma tHcy concentrations were -20.9%, -13.1%, and -7.1% in persons with the T/T, C/T, and C/C genotypes, respectively (P = 0.019 for T/T compared with C/C. Figure 1). The decreases in plasma tHcy concentrations were not significantly different for subjects receiving 1 compared with 2 mg folic acid/d. Subjects who were previously taking multivitamins experienced smaller decreases in plasma tHcy concentrations after folic acid supplementation, but the T/T homozygotes still showed a trend for greater responsiveness than the C/C or C/T subjects (changes in plasma tHcy concentrations: -10.2%, -3.3%, and -3.2% for T/T, C/T, and C/C genotypes, respectively; NS) (2). Geometric mean plasma tHcy concentrations among T/T, C/T, and C/C subjects were not significantly different after folic acid supplementation. Thus, although individuals with the T/T genotype had higher plasma tHcy concentrations at baseline, our results suggest that these individuals were more sensitive to the tHcy-lowering effects of folic acid supplementation. The reasons for the disparities among the results of these studies are unknown, but additional investigations, including further analyses of the

data from Woodside et al, may help to elucidate possible contributory factors.

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REFERENCES