Treatment of hyperhomocysteinemia in hemodialysis patients and renal transplant recipients.

Bostom AG, Shemin D, Goih RY, Beaulieu AJ, Bagley P, Massy ZA, Jacques PF, Dworkin L, Selhub J.

Division of General Internal Medicine, Memorial Hospital of Rhode Island, Pawtucket 02860, USA. abostom@loa.com

BACKGROUND: Hyperhomocysteinemia, a putative atherothrombotic risk factor, is observed in at least 85% of patients undergoing maintenance hemodialysis (HD), as well as 65 to 70% of renal transplant recipients (RTRs). The hyperhomocysteinemia regularly found in HD patients is largely refractory to combined oral vitamin B supplementation featuring supraphysiological doses of folic acid (FA). Relative to their HD counterparts, the hyperhomocysteinemia of RTRs appears to be considerably less refractory to treatment with high-dose FA-based vitamin B supplementation regimens, although controlled comparison data are lacking. We evaluated whether improved total homocysteine (tHcy)-lowering efficacy could be achieved in chronic HD patients with a high-dose L-5-methyltetrahydrofolate (MTHF)-based regimen, as suggested by recent uncontrolled findings, and compared the relative responsiveness of RTRs and HD patients with equivalent baseline tHcy levels, to 12 weeks of tHcy lowering with combined folate-based vitamin B treatment. METHODS: First, we blocked randomized 50 chronic, stable HD patients based on their screening predialysis tHcy levels, sex, and dialysis center into two groups of 25 subjects treated for 12 weeks with oral FA at 15 mg/day, or an equimolar amount (17 mg/day) of oral MTHF. All 50 subjects also received 50 mg/day of oral vitamin B6 and 1.0 mg/day of oral vitamin B12. RESULTS: The mean percentage (% reductions (+/- 95% confidence intervals) in predialysis tHcy were not significantly different [MTHF 17.0% (12.0 to 22.0%), FA 14.8% (9.6 to 20.1%), P = 0.444 by matched analysis of covariance adjusted for pretreatment tHcy]. Final on-treatment values (mean with 95% confidence interval) were: MTHF, 20.0 micromol/L (18.8 to 21.2); and FA, 19.5 micromol/L (18.3 to 20.7). Moreover, neither treatment resulted in "normalization" of tHcy levels (that is, final on-treatment values...
<12 micromol/L) among a significantly different or clinically meaningful number of patients [MTHF, 2 out of 25 (8%); FA, 0 out of 25 (0%); Fisher's exact test of between groups difference, P = 0.490]. Second, we compared the relative responsiveness of (N = 10) RTRs and (N = 39) HD patients with equivalent baseline tHcy levels (RTR range of 14.2 to 23.6 micromol/L, and HD range of 14.4 to 24.9 micromol/L) to 12 weeks of tHcy-lowering treatment. The RTRs received 2.4 mg/day of FA, 50.0 mg/day of vitamin B6, and 0.4 mg/day of vitamin B12, while the HD patients received 15 mg/day of FA or an equimolar amount (17 mg/day) of the reduced folate, MTHF, in addition to 50.0 mg/day of vitamin B6 and 1.0 mg/day of vitamin B12. The mean percentage (%) reductions (+/- 95% confidence interval) in tHcy were as follows: RTR 28.1% (16.2 to 40.0%); HD 12.1% (6.6 to 17.7%, P = 0.027 for comparison of between groups differences by analysis of covariance adjusted for baseline tHcy levels). Moreover, 5 out of 10 (50.0%) of the RTR versus only 2 out of 39 (5.1%) of the HD patients had final on-treatment tHcy levels <12 micromol/L (P = 0.002 for comparison of between groups differences by Fisher's exact test). CONCLUSIONS: First, in comparison to high-dose FA, high-dose oral MTHF-based supplementation does not afford improved tHcy-lowering efficacy among HD patients. The preponderance of HD patients (that is, > 90%) exhibits mild hyperhomocysteinemia refractory to treatment with either regimen. This treatment refractoriness is not related to defects in folate absorption or circulating plasma and tissue distribution. Second, relative to RTR with comparable baseline tHcy levels, the mild hyperhomocysteinemia of maintenance HD patients is much more refractory to tHcy-lowering vitamin B treatment regimens featuring supraphysiological amounts of FA or the reduced folate MTHF. Accordingly, RTRs are a preferable target population for controlled clinical trials testing the hypothesis that tHcy-lowering vitamin B intervention may reduce arteriosclerotic cardiovascular disease event rates in patients with chronic renal disease.