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Lifestyle effects on homocysteine and an alcohol paradox[1,2]

Charles H Halsted

The article by Koehler et al (1) in this issue of the Journal points out the complexity of causes of elevated total homocysteine concentrations (tHcy) in serum and, in particular, raises interesting issues concerning the relation of alcohol consumption to hyperhomocysteinemia. With the goal of defining the regulation of tHcy in aging, Koehler et al studied a cross section of 278 healthy elderly subjects living in New Mexico (mean age: 76 y); 61% of the subjects were women, 61% consumed an average of 21 alcoholic drinks/mo (<1 to >2 drinks/d), and 65% used daily supplemental vitamins containing folic acid (400 μg), vitamin B-12 (6–25 μg), and vitamin B-6 (2–3 mg). Importantly, the study was performed in 1993, well before the advent of folic acid fortification of the US grain supply.

After evaluating the data by linear multivariate analysis, the authors found that a significant inverse relation between tHcy and folate intake was limited to nonusers of supplements and that increasing age, serum creatinine, male sex, smoking (among only 3% of the group), and coffee or tea consumption ($\bar{x}$: 2.3 cups/d) were all related to moderate increases in tHcy. Among the 168 users of alcoholic beverages, the nonquantified overall use of alcohol augmented the tHcy-lowering effect of food folate in those not taking vitamin supplements. However, when the data were broken down by quartiles, tHcy was significantly higher (by 1.3 μmol/L) in those consuming >60 drinks/mo (>2 drinks/d) than in those consuming <30 drinks/mo (<1 drink/d).

These new lifestyle findings complement 2 other studies. The Norwegian Hordaland Homocysteine Study of 11 941 healthy middle-aged adults who did not take folic acid supplements found that age, male sex, smoking, and coffee consumption were all significant positive determinants of tHcy, whereas food folate was a significant inverse determinant (2). A 1993 study of 260 retired schoolteachers in Baltimore (mean age: 64 y) showed that coffee consumption and serum creatinine were positive predictors of tHcy, whereas dietary protein, food folate, and supplemental folic acid all had inverse effects on tHcy (3). In summary, all 3 studies suggest that the tHcy value must be interpreted in light of multiple factors in addition to folate intake, including male sex, increasing age, serum creatinine, smoking status, coffee or tea consumption, and use of alcoholic beverages. Conceivably, the known associations of each of these lifestyle factors on cardiovascular disease risk may be mediated through effects on tHcy. Also, the modulating effect of each factor must be considered when establishing the relation of one or more genetic effects in folate metabolism and the methionine-homocysteine cycle to hyperhomocysteinemia.

Many prior studies established an antagonistic effect of excessive alcohol use on folate metabolism (4) and it is known that even moderate use of alcohol together with a relatively low-folate diet carries a 3-fold increased risk of colon cancer in men (5). On the other hand, many other studies (also summarized in reference 4) showed a J-shaped effect of alcohol consumption on all-cause mortality, with the lowest mortality in those consuming moderate amounts (1–2 drinks/d). From these studies it appears that alcohol consumption has a protective effect on coronary artery disease, but that noncardiac mortality from hemorrhagic strokes, cancer, and alcoholic liver disease increases with alcohol consumption beyond moderate levels. In this context, the finding by Koehler et al (1) of a J-shaped relation between tHcy and alcohol consumption suggests a new tHcy-lowering mechanism for cardiovascular protection during moderate alcohol consumption. This finding complements prior data from the Nurses' Health Study showing that the protective effect of a high-folate diet on coronary artery disease in women was augmented in those consuming ≤2 alcoholic drinks/d (6). The relations among folate intake, alcohol consumption, tHcy, and coronary risk could be further explored with a greater number of subjects and more precise quantification of alcohol intake with multivariate analysis of all other factors that modify tHcy.

In contrast with a potential benefit of moderate alcohol consumption on tHcy and coronary artery disease risk, others found marked elevations in tHcy among excessive alcohol consumers. The tHcy concentration increased ≥45 μmol/L in 42 patients admitted for alcohol intoxication in Malmo, Sweden, and fell to a normal range after 15 d, whereas tHcy was in the normal range in 16 abstinent alcoholics (7). In another study, 32 actively drinking chronic alcoholics from Lisbon had significantly lower concentrations of vitamin B-6 and red blood cell folate and 2-fold higher tHcy concentrations up to a concentration of 40 μmol/L than did healthy control subjects (8). These observations suggest an alcohol-homocysteine paradox, whereby alcohol consumption, known to be cardioprotective (4), elevates tHcy, which is a known cardiovascular disease risk factor. Although further confirmation is needed, the paradox may be resolved by the present observation that moderate alcohol consumption of <2 drinks/d lowers tHcy, whereas greater alcohol consumption increases tHcy (1).

Finally, what mechanisms account for this dual effect of alcohol consumption on tHcy? Data from 4 different animal models clearly show effects of excessive alcohol intake on the methionine cycle

[1] From the University of California Davis.

[2] Address reprint requests to CH Halsted, University of California, *The American Journal of Clinical Nutrition*, 3247 Meyer Hall, One Shields Avenue, Davis, CA 95616-8790.

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(9–12). The earliest and perhaps classic study showed opposing effects of gastric intubation of 50% alcohol (4.4 g/kg body wt) with a low-casein diet on hepatic methionine cycle enzymes, including potentially tHcy-lowering increases in *S*-adenosylmethionine (SAM) synthetase (methionine adenosyltransferase), cystathionine β-synthase, and betaine–homocysteine *S*-methyltransferase, but a counteracting tHcy-elevating decrease in 5-methyltetrahydrofolate–homocysteine *S*-methyltransferase (methionine synthase) (9). Two other studies confirmed the increase in hepatic betaine–homocysteine *S*-methyltransferase and decrease in methionine synthase in chronic ethanol-fed rats (10, 11), one also showing a decrease in hepatic SAM and an increase in *S*-adenosylhomocysteine (11). Our later study of micropigs fed alcohol at 40% of energy with an excess of dietary folate showed a progressive rise in serum tHcy to twice control concentrations, together with significant inhibition of methionine synthase and decreases in the hepatic ratio of SAM to *S*-adenosylhomocysteine after 12 mo (12). Thus, the real alcohol paradox remains the apparent dual effect of alcohol to lower tHcy when consumed in moderate amounts but to increase tHcy when consumed in excessive amounts. This paradox may be explained by further and more refined experiments on the effects of varied alcohol intake on folate and tHcy concentrations and the multitude of reactions controlling the hepatic methionine and homocysteine metabolic cycle.

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