A healthy lifestyle lowers homocysteine, but should we care?1–3

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A high plasma concentration of total homocysteine (tHcy), a sulfur-containing amino acid, predicts an elevated risk of cardiovascular disease and possibly of dementia (1). High tHcy concentrations can be due to many factors, such as a low intake of folate or vitamin B-12, poor kidney function, or a common mutation in the folate-metabolizing enzyme methylenetetrahydrofolate reductase.

In this issue of the Journal, Nurk et al (2) report findings from the Norwegian, population-based Hordaland cohort, in which they examined whether changes in lifestyle predict changes in tHcy concentration. At baseline, median tHcy concentrations varied from 8.8 μmol/L in the women aged 41–42 y to 11.9 μmol/L in the men aged 65–67 y. After 6 y of follow-up, median tHcy concentrations decreased 0.1 μmol/L in the younger subjects and increased 0.4 μmol/L in the older subjects. As expected, changes in vitamin supplement use and in plasma folate and vitamin B-12 concentrations showed strong associations with changes in tHcy concentration over time, but changes in smoking and coffee consumption also affected tHcy concentrations. Interestingly, an increase in body weight—≈3 kg, on average, in the subjects aged 41–42 y—was associated with a decrease in tHcy concentration.

In 1995 and 1997, the Hordaland Homocysteine Study drew attention to smoking and coffee consumption as determinants of tHcy concentration. The effect of coffee was later confirmed in experiments, which showed that 4 wk of drinking 6 cups of strong filtered coffee/d increased tHcy concentrations ≈20% (3). The effect of coffee appeared to be due to caffeine and chlorogenic acid, both of which are common ingredients in coffee. Cessation of coffee drinking reversed these increases in tHcy concentration. Homocysteine concentrations are also ≈20% higher in smokers than in nonsmokers (4), but whether this is due to something in tobacco or to poor dietary habits associated with smoking is not yet clear. Folic acid supplementation decreases tHcy concentrations ≈10–30% depending on dose and initial tHcy concentration. Thus, stopping coffee drinking and possibly smoking could decrease tHcy concentrations as much as taking a B vitamin supplement does.

Obviously, the effects of changes in lifestyle on changes in tHcy concentration in the article by Nurk et al were much smaller than those observed under experimental conditions. This can be explained by several factors. First, the lifestyle changes were probably smaller than those in experiments. For example, a typical daily dose of folic acid in experiments is 400 μg, whereas the additional intake in the Norwegian multivitamin supplement users was ≈50 μg/d because supplements were often taken only a few times per week and contained only 100 or 200 μg folic acid per tablet. Second, errors in measuring lifestyle factors also dilute associations with changes in tHcy concentration.

The unexpected association between weight gain and a decrease in tHcy concentration could be due to confounding but could also mean that weight loss increases tHcy concentrations. Unfortunately, randomized weight-loss trials are plagued by high numbers of dropouts and lack of blinding, and as a result, remarkably little is known about the long-term health effects of weight reduction, including effects on tHcy concentrations. One study compared 293 subjects who had been losing weight for ≥1 y after gastric restrictive surgery with patients who had not yet undergone this surgery (5). The group who had been losing weight had higher tHcy concentrations: 10.4 compared with 9.2 μmol/L. A Chinese study (6) also observed an ≈2-μmol/L increase in tHcy concentration 1 y after gastroplasty. In both studies, the increase in tHcy concentration was not explained by decreased folate or vitamin B-12 concentrations. If weight reduction truly increases tHcy concentrations, we need to find out whether the loss in fat mass per se, related metabolic effects, or the weight-reducing diet itself leads to this increase. For example, the Atkins diet could increase tHcy concentrations because it is high in protein and thus methionine, which is the precursor of tHcy.

Thus, reducing coffee consumption or taking a multivitamin supplement containing folic acid reduces tHcy concentrations in most persons, and cessation of smoking might also help. However, should we really worry about modest elevations in tHcy concentration? Their causal link with the risk of vascular disease is supported by the fact that subjects whose tHcy concentrations are elevated through a mutation in the gene for methylenetetrahydrofolate reductase are at increased risk of coronary artery disease (7). However, recent randomized trials did not show a reduction in cardiovascular disease after treatment with B vitamins. The second Cambridge Heart Antioxidant Study (CHAOS-2), in which 1882 patients received folic acid or pla...
cebo for 1.7 y showed a 13% reduction in tHcy concentration but no reduction in coronary artery disease or major vascular events (8). In the Vitamin Intervention for Stroke Prevention (VISP) trial, 3680 stroke patients with elevated tHcy concentrations were randomly assigned to receive either a high dose or a low dose of B vitamins for almost 2 y. The high-dose vitamin treatment was associated with a 15% reduction in tHcy concentration but had no effect on the risks of recurrent stroke or coronary artery disease events (9). A third, German and Dutch trial assessed the rate of restenosis after stent implantation in coronary arteries in patients who were randomly assigned to receive either B vitamins or placebo for 6 mo (10). This trial showed that B vitamins increase the rate of restenosis.

These early trials were all underpowered and may therefore have missed a beneficial effect of B vitamins. However, even if the upcoming large trials with B vitamins show protective effects, whether tHcy is causally involved will remain uncertain (Figure 1). In other words, even if folic acid protects against coronary artery disease, tHcy could be on a metabolic side path, and the tHcy-increasing effect of coffee, for example, could still be innocuous. Only a clinical trial in which tHcy concentrations are decreased by means other than B vitamins, eg, by betaine (11), could settle this issue. Until that time, we should realize that a high tHcy concentration may just be a marker of low vitamin status, subclinical renal atherosclerosis, or an unhealthy lifestyle rather than a true causal risk factor.

REFERENCES