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EDITORIAL

Homocysteine—an indicator of a healthy diet?[1,2]

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INTRODUCTION

Halfway through the past century, experiments in humans showed that a high dietary intake of saturated fat increased blood concentrations of cholesterol, which was later proven to be a key risk factor for cardiovascular disease (CVD). In the 1960s, the first epidemiologic studies pointed to another potential risk factor for CVD: high serum concentrations of total homocysteine (tHcy), a sulfur-containing amino acid derived from methionine. Epidemiologic data accumulated rapidly, and homocysteine became notorious as "the cholesterol of the 1990s." Now—as if it were a self-fulfilling prophecy—high saturated fat intake may also be associated with higher tHcy concentrations, according to data from the Hordaland Homocysteine Study, as reported by Berstad et al in this issue of the Journal (1). In that cross-sectional, population-based study of 5917 subjects in 2 age groups (47–49 and 71–74 y old), a 12–15-g higher intake of saturated fat was associated with ≈6% higher tHcy concentrations, after adjustment for sex, age group, energy intake, daily smoking, coffee drinking, and folate intake. This association is of the same magnitude as the association that can be predicted between saturated fat intake and LDL cholesterol by using the formula provided by Mensink et al (2). Furthermore, the authors found that the intake of marine very-long-chain (VLC) n–3 fatty acids (FAs) was inversely associated with serum concentrations of tHcy.

These data are intriguing, but they raise several questions. Were the analyses sufficiently adjusted for potential confounding factors that are linked to both fat intake and tHcy concentrations? Are these findings supported by data from dietary intervention studies? What mechanisms could explain the observed associations? And last (but not least), is the notorious reputation of tHcy as a mediator of multiple phenomena still justified?

Berstad et al showed that tHcy appears to be a good marker of "adherence to dietary guidelines": subjects using vegetable oils, drinking low-fat or skimmed milk, avoiding cream, and taking fish-oil supplements had lower tHcy concentrations. These subjects are very likely also to have adhered to guidelines for the intakes of fruit and vegetables (3). The latter are good sources of folate, which is known to lower tHcy. Hence, initial positive associations between fat intake and tHcy were weakened or were no longer significant after adjustment for the intakes of vegetables and fruit or B vitamins.

Insufficient control for confounding is a worry with respect to every study of associations between diet and disease. No matter how thoroughly it may be done, adding confounding variables to a regression model is no guarantee for unbiased data, simply because certain confounding factors either are not measured or are imperfectly measured. On the other hand, observed associations may also reflect true underlying relations. For example, in the same Norwegian study population that Berstad et al used, a strong positive association between the consumption of filtered coffee

and tHcy concentrations (4) was confirmed by several later experiments (5).

As reviewed by Berstad et al, the inverse association of VLC n−3 FA intake with tHcy concentrations is backed up by data from some but not all intervention studies. Results of an intervention study conducted by Appel et al (6) provide limited evidence for a link between saturated fat intake and tHcy. In that study, 118 participants started with a 3-wk control diet low in fruit and vegetables and high or normal in dairy products, including a saturated fat content that was typical of US consumption. During an 8-wk intervention phase, the participants were then fed 1 of 3 randomly assigned diets: the control diet, a diet rich in fruit and vegetables but otherwise similar to the control diet, or a diet rich in fruit, vegetables, and low-fat dairy products and low in saturated and total fats. The third diet led to a reduction in tHcy concentrations, whereas the diet rich in fruit and vegetables but still high in saturated fats did not.

The observed associations between the intake of FAs and tHcy concentrations may be explained by a biochemical link between homocysteine metabolism and phopholipid metabolism (7, 8): homocysteine is formed during the *S*-adenosylhomocysteine–dependent methylation of phosphatidylethanolamine to phosphatidylcholine, which is catalyzed by phosphatidylethanolamine methyltransferase (PEMT). The existence of this biochemical link between homocysteine and phospholipid metabolism is supported by an animal study suggesting that increasing the saturation of FAs in the diet increases the synthesis of phosphatidylcholine via the PEMT pathway (9).

Surprisingly, the inverse association of VLC n−3 FAs with serum concentrations of tHcy, as found by Berstad et al, existed only among the upper 25% of subjects with high intake of B vitamins. The authors concluded that this finding fit well with an earlier proposed hypothesis of de Bree et al (10) that high intakes of n−3 FAs may reduce tHcy only in combination with high B vitamin intake. However, de Bree et al concluded only that a combined intervention of B vitamins and n−3 FAs may be more effective in reducing the risk of CVD than may either of those treatments alone. It is worrisome that the inverse association of VLC n−3 FAs with tHcy was found only in a subgroup with high intake of B vitamins, because that finding may again point to insufficient control for confounding.

Is there any consensus yet on whether elevated tHcy is truly a cause of CVD? High tHcy correlates with the risk of CVD in epidemiologic studies, but findings from most secondary prevention studies do not show that lowering of tHcy by B vitamins is beneficial. Some researchers may say that homocysteine could be involved in the very early stages of atherosclerosis, which leaves the door open for primary prevention by B vitamin supplementation. However, it is hardly feasible to test this hypothesis in trials. At this time, I would consider high tHcy to be a marker of an imprudent diet, which may in fact explain its association with a greater risk of CVD. I propose that we put further effort into investigating the possible role of VLC n−3 FAs in preventing heart disease, be it via the lowering of tHcy or some other mechanism. And, finally, let us look further into the possible beneficial role of folic acid in preventing age-related diseases such as cognitive decline (11, 12).

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REFERENCES

1. Berstad P, Konstantinova SV, Refsum H, et al. Dietary fat and plasma total homocysteine concentrations in 2 adult age groups: the Hordaland Homocysteine Study. Am J Clin Nutr 2007;85:1598-605.[Abstract/Free Full Text]
2. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. Am J Clin Nutr 2003;77:1146–55.[Abstract/Free Full Text]
3. Agudo A, Pera G. Vegetable and fruit consumption associated with anthropometric, dietary and lifestyle factors in Spain. EPIC Group of Spain. European Prospective Investigation into Cancer. Public Health Nutr 1999;2:263–71.[Medline]
4. Nygard O, Refsum H, Ueland PM, et al. Coffee consumption and plasma total homocysteine: the Hordaland Homocysteine Study. Am J Clin Nutr 1997;65:136–43.[Abstract/Free Full Text]
5. Urgert R, van Vliet T, Zock PL, Katan MB. Heavy coffee consumption and plasma homocysteine: a randomized controlled trial in healthy volunteers. Am J Clin Nutr 2000;72:1107–10.[Abstract/Free Full Text]
6. Appel LJ, Miller ER III, Jee SH, et al. Effect of dietary patterns on serum homocysteine: results of a randomized, controlled feeding study. Circulation 2000;102:852–7.[Abstract/Free Full Text]
7. Jacobs RL, Stead LM, Devlin C, et al. Physiological regulation of phospholipid methylation alters plasma homocysteine in mice. J Biol Chem 2005;280:28299–305.[Abstract/Free Full Text]
8. Olthof MR, van Vliet T, Verhoef P, Zock PL, Katan MB. Effect of homocysteine-lowering nutrients on blood lipids:

results from four randomised, placebo-controlled studies in healthy humans. PLoS Med 2005;2:e135.[Medline]
9. Hargreaves KM, Pehowich DJ, Clandinin MT. Effect of dietary lipid composition on rat liver microsomal phosphatidylcholine synthesis. J Nutr 1989;119:344–8.[Abstract/Free Full Text]
10. de Bree A, Mennen LI, Hercberg S, Galan P. Evidence for a protective (synergistic?) effect of B-vitamins and omega-3 fatty acids on cardiovascular diseases. Eur J Clin Nutr 2004;58:732–44.
11. Durga J, van Boxtel MP, Schouten EG, et al. Effect of 3-year folic acid supplementation on cognitive function in older adults in the FACIT trial: a randomised, double blind, controlled trial. Lancet 2007;369:208–16.[Medline]
12. Clarke R. Homocysteine, B vitamins, and the risk of dementia. Am J Clin Nutr 2007;85:329–30 (editorial). [Free Full Text]

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