Betaine Supplementation and Blood Lipids: Fact or Artifact?

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Betaine supplementation in humans has been shown to lower plasma homocysteine concentrations in modestly hyperhomocysteinemic patients. Betaine treatment is associated with increased plasma low-density-lipoprotein (LDL) cholesterol, suggesting that although betaine supplementation lowers homocysteine, a risk factor for cardiovascular disease, changes in blood lipids may have a counterbalancing effect. However, whether the betaine effect on LDL concentration is a clinically significant problem that should change treatment options or is simply an artifact needs further study.

The biological rationale for folate or betaine therapy in homocysteinemic patients is that homocysteine can be methylated to form methionine\(^1\) by two parallel pathways (Figure 1), both of which lower homocysteine concentrations.\(^2\) In the first, vitamin B\(_{12}\) and folic acid are involved in a reaction catalyzed by methionine synthase.\(^3\) Deficiency of these nutrients\(^4,5\) or single-nucleotide polymorphisms in the genes for the enzymes involved in this pathway\(^3,5,6\) can result in elevated plasma homocysteine concentrations. The alternative pathway for the methylation of homocysteine to form methionine is catalyzed by betaine homocysteine methyltransferase,\(^7\) an enzyme whose activity has been reported to increase in rats during methionine excess.\(^8\) Betaine, derived from dietary choline by the action of choline dehydrogenase, is the methyl group donor in this reaction, and supplemental oral betaine can lower plasma homocysteine concentrations.\(^9,10\)

Recently, Olthof et al.\(^11\) examined two nutrient-based approaches for lowering plasma homocysteine concentrations in modestly hyperhomocysteinemic patients. While both betaine (1.5, 3, or 6 g/d) and folic acid (0.8 mg/d) treatment for 6 weeks lowered plasma homocysteine by 12% to 20%, betaine treatment was associated with increased plasma low-density lipoprotein (LDL) cholesterol concentrations. This effect showed a dose-response relationship, with those treated with 1.5 g/d betaine having an increase in LDL relative to placebo treatment of 0.1 mmol/L; 3 g/d having an increase of 0.2 mmol/L; and 6 g/d having an increase of 0.4 mmol/L. This was not observed with folate treatment. The authors concluded that betaine treatment lowers homocysteine, but increases LDL cholesterol, thereby counterbalancing its effectiveness in lowering the risk for cardiovascular disease. They recommended that folate therapy be used instead.

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Before accepting the recommendations made by Olthof et al.,\(^11\) a closer examination of their findings is justified. They used data on response to betaine collected in two separate studies. In study 1, LDL cholesterol in the placebo group started at 3.36 mmol/L and dropped at 6 weeks to 3.05 mmol/L; in study 2, the placebo group started at 3.17 mmol/L and finished at 3.05 mmol/L. In study 1, the betaine group started at LDL concentration of 3.02 mmol/L and finished at 3.34 mmol/L; in study 2 they started at 2.88 mmol/L and finished at 3.02 mmol/L. In study 1, the betaine group started at LDL concentration of 3.02 mmol/L and finished at 3.34 mmol/L; in study 2 they started at 2.88 mmol/L and finished at 3.02 mmol/L. Thus, in the first study, the treated group started out at much lower LDL concentrations than did placebo, and after treatment had LDL concentrations virtually identical to the placebo group at the start of the study. The statistical significance arose because the placebo group had decreased LDL concentrations after 6 weeks.

Why would a placebo have this effect? In study 2, the betaine-treated group started with lower LDL cholesterol concentrations than the placebo group and ended up with identical concentrations. The statistical effect
appears to have been due to a difference in randomization of the subjects. The baseline LDL values for the folate-treated group in study 1 were 3.12 mmol/L—again, like placebo, higher than the baseline for the betaine-treated group. After 6 weeks of treatment, the folate-treated groups ended up at LDL concentrations of 3.19 mmol/L, just modestly lower than the 3.34 mmol/L reported for the betaine-treated subjects. Is the difference between betaine treatment and folate treatment on LDL concentrations fact or artifact?

A POSSIBLE MECHANISM OF BETAINE EFFECTS ON LDL CHOLESTEROL

Given that there was a dose-response relation for the betaine effect on LDL, there may be a plausible biological mechanism. The most likely explanation derives from the need for a phosphatidylcholine moiety to secrete very-low-density lipoprotein (VLDL, a precursor of LDL) from liver. The VLDL particle is wrapped in a membrane containing phosphatidylcholine, and when this is not available, cholesterol and triglyceride move to the cytosol, thus causing fatty liver.12-14 There is a rapid response to changes in choline availability: lipid accumulation within hepatocytes begins within hours after rats are started on a choline-deficient diet.15 Choline-deficient humans have diminished plasma LDL16 and an exaggerated rise in plasma homocysteine when given a dietary methionine load.17 Betaine is formed from choline, and perhaps betaine treatment spares this use of choline so that more is available for phosphatidylcholine biosynthesis in liver, thereby making more available for VLDL formation.

The subjects in the Olthof study11 had high homocysteine concentrations, and it is possible that they were marginally low in choline and the betaine therapy corrected this. If so, the LDL increase observed in the betaine-treated subjects could be attributed to mobilization of cholesterol and triglyceride from the cytosol of fatty liver to plasma, which is not an adverse outcome. However, it is difficult to understand why treatment with phosphatidylcholine was not associated with increased LDL concentrations. Note that in this latter study, both placebo and phosphatidylcholine-treated groups had LDL concentrations of 3.6 mmol/L, which was significantly higher than the final concentrations achieved in the betaine-treated groups of studies 1 and 2. Again, was the betaine effect on LDL concentrations a clinically significant problem that should change treatment options or merely an artifact that should not? This work was funded by a grant from the National Institutes of Health (DK55865, AG09525, ES012997) and the USDA (2004-01833). Support for this work was also provided by grants from the NIH to the UNC General Clinical Research Center (RR00046), and the Center for Environmental Health and Susceptibility (ES10126).

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