Effect of Folic Acid Supplementation on Inflammatory Markers

Durga J, van Tits LJ, Schouten EG, et al. Effect of lowering of homocysteine levels on inflammatory markers: a randomized controlled trial. Arch Intern Med 2005;165:1388–94.

Study Overview

Objective. To investigate the effect of folic acid supplementation on homocysteine concentrations and markers of inflammation.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. 530 patients aged 50 to 70 years from the Netherlands with serum homocysteine concentrations of 1.8 mg/L or higher were randomized to receive folic acid supplementation (0.8 mg/d) or placebo for 1 year.

Main outcome measures. Serum concentrations of homocysteine, folic acid, C-reactive protein (CRP), soluble intracellular adhesion molecule-1 (ICAM1), oxidized low-density lipoprotein (LDL), and autoantibodies against oxidized LDL.

Main results. At 1 year, serum folate concentrations increased by 400% (95% confidence interval [CI], 362%–436%) and homocysteine concentrations decreased by 28% (95% CI, 24%–36%) in the folic acid group compared with the placebo group. However, no changes in plasma concentrations of the inflammatory markers were observed.

Conclusion. Although homocysteine is associated with vascular disease risk in the general population, marked lowering of slightly elevated homocysteine concentrations using folic acid supplementation for 1 year does not influence inflammatory responses involving CRP, soluble ICAM1, oxidized LDL, and autoantibodies against oxidized LDL.

Commentary

Homocysteine is a highly reactive, sulfur-containing amino acid formed as a by-product of methionine metabolism. Cells remetabolize homocysteine by a number of pathways that involve several different enzymes; these enzymes variously use B vitamins (folate, cobalamin [vitamin B_{12}], and pyridoxine [vitamin B_6]) as substrates or cofactors. Homocysteine levels in the blood are strongly influenced by diet and genetic factors.

Studies have reported an association between homocysteine levels and vascular risk in both the general population and in those with preexisting vascular disease. A number of meta-analyses have been performed in recent years in an attempt to summarize the evidence [1,2]. In general, prospective studies in healthy persons have presented weaker evidence for the association between homocysteine and cardiovascular disease. So far, no controlled treatment study has shown that folic acid supplements reduce the risk of atherosclerosis or that taking B vitamins affects the development or recurrence of cardiovascular disease; however, trials are ongoing.

Durga et al sought to determine if the pathogenic mechanism of elevated concentrations of homocysteine occurs through inflammation (by examination of CRP and ICAM1 levels) or oxidation (oxidized LDL levels). They note that "the possible pathogenic mechanism remains unsolved, and convincing evidence to support a causal relationship between elevated concentrations of homocysteine and risk of heart disease is absent." A limitation to this study is that lowering homocysteine concentrations may affect other inflammatory markers or pathways that lead to vascular disease in the presence of atherosclerosis.

Applications for Clinical Practice

The Canadian Task Force on Preventive Health Care completed an evidence-based review of the association of elevated homocysteine levels and coronary artery disease and treatment of homocysteine levels with vitamin supplementation or diet [3]. This process yielded results of an association between total homocysteine levels and cardiovascular risk. Currently, however, there is insufficient evidence to make recommendations regarding treatment with folic acid supplementation in the general population.

–Review by Christianne L. Roumie, MD, MPH

"Outcomes Research in Review" is edited by Stephen D. Persell, MD, MPH, Department of Medicine, Northwestern University, Chicago, IL; Harvey J. Murff, MD, MPH, and Christianne L. Roumie, MD, MPH, Division of General Internal Medicine, Vanderbilt University Medical Center, Nashville, TN; David R. Spigel, MD, Sarah Cannon Research Institute, Nashville, TN; and Thomas D. Sequist, MD, MPH, and Mark S. Horng, MD, Division of General Medicine, Brigham and Women's Hospital, Boston, MA.

References

1. Hackam DG, Anand SS. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. JAMA 2003;290:932–40.
2. Homocysteine Studies Collaboration. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. JAMA 2002;288:2015–22.
3. Booth GL, Wang EE. Preventive health care, 2000 update: screening and management of hyperhomocysteinemia for the prevention of coronary artery disease events. The Canadian Task Force on Preventive Health Care. CMAJ 2000; 163:21–9.