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CLINICAL INQUIRIES FROM THE FAMILY PRACTICE INQUIRIES NETWORK

Is folate supplementation indicated for patients with CAD?

Kerri Hecox, MD Wayne Hale, MD

Department of Family Medicine, Moses Cone Memorial Hospital, Greensboro, NC

Leslie Mackler, MSLS

Moses Cone Health System, Greensboro, NC

EVIDENCE-BASED ANSWER

There is insufficient evidence to advocate the routine use of folate supplementation for the treatment of coronary artery disease (CAD). High levels of serum homocysteine have been associated in several studies with an increased risk for CAD (strength of recommendation [SOR]: **B**, associated in case-control studies). Folate supplementation decreases the level of serum homocysteine (SOR: **A**, meta-analysis of randomized controlled trials). This indirect evidence suggests that folate supplementation may be of benefit in slowing the progress of arteriosclerosis.

Two randomized controlled trials measuring the clinical benefits of folate supplementation for patients with CAD have been completed, with differing results. One study showed no benefit of 0.5 mg/d of folate for patients with stable CAD already on statin therapy. The other study found that patients given 1 mg/d of folate with vitamins B_6 and B_{12} had a decreased restenosis rate after percutaneous coronary intervention (PCI) (SOR: **B**, conflicting randomized controlled trials).

It is possible that larger doses of folate are needed to be of clinical benefit, or that the addition of vitamins B_6 and B_{12} are needed for synergy. Several randomized control trials are underway to further assess folate's affect on CAD.

EVIDENCE SUMMARY

Hyperhomocysteinemia is defined as a fasting plasma homocysteine level 15 µmol/L, although levels >10 µmol/L appear to have detrimental effects on risk profiles for CAD and arteriosclerosis.[1] In 22 of 27 retrospective case-control studies, patients with CAD had significantly higher plasma homocysteine levels than control subjects (odds ratio [OR]=1.2–10.9, after adjustment for other CAD risk factors).[2,3] However, only 4 of 7 prospective nested case-control trials showed a correlation between elevated homocysteine and myocardial infarction (MI) and coronary death.[2]

A meta-analysis of 12 randomized controlled trials found that folate supplementation, with vitamin B_6 and B_{12}, reduces plasma homocysteine levels.[4] However, the long-term clinical cons quences of these interventions are unknown. At doses of 1 gm/d folate has no known side-effects.[5]

Two randomized, placebo-controlled trials of folate reporting clinical endpoints have been completed. One study analyzed folate supplementation in a patient population with known, stable CAD and found no difference in clinical endpoints at 24 months.[6] In this study, 593 patients were randomized to receive either 0.5 mg/d of folic acid or placebo. The primary study endpoint was a composite of events including: overall mortality, sudden death, MI, stroke, and major vascular surgery. The study was powered to detect a 50% reduction in clinical events based on existing observational data in populations with CAD. An event rate of 15% for the 2-year interval was assumed.[6] All patients in this study were on statin therapy prior to initiation of folate supplementation.

The second study analyzed folate supplementation in 553 post-PCI patients. Patients were treated with 1 mg of folate plus 10 mg of vitamin B_6 and 400 µg of vitamin B_{12} for 6 months after the PCI. After a mean follow-up of 11 months, the rate of restenosis requiring revascularization was lower in the vitamin-treated study arm (9.9% vs 16% restenosis rate; relative risk [RR]=0.62; 95% confidence interval [CI], 0.40–0.97; number needed to treat=16).[7] There was also a nonsignificant trend toward fewer deaths and MIs in the treated arm at both 6 and 12 months after intervention (*death:* 1.5% vs 2.8%; RR=0.54; 95% CI, 0.016–1.7; *MI:* 2.6% vs 4.3%; RR=0.60; 95% CI, 0.24–1.51). Statin use was similar in both control (71%) and treatment groups (69%).

RECOMMENDATIONS FROM OTHERS

The American Heart Association and American College of Cardiology do not recommend the routine use of high-dose folic acid or B-vitamin supplements for the primary or secondary prevention of cardiovascular events. The AHA recommendation is to meet recommended daily allowances of folate (400 µg), B_{12} (2.4 µg), and B_6 (1.7 mg) primarily through a balanced diet, with use of supplements if diet alone does not meet the above requirements.[8] Since 1998, wheat flour has been supplemented with folate, adding an estimated 100 µg/day to the average American diet.[8]

The Canadian Task Force on Preventive Health Care (CTFPHC) finds insufficient evidence to advocate screening for hyperhomocysteinemia and rely on expert opinion to advocate treatment in select, high-risk populations.[2] Currently, the CTFPHC advocates meeting the recommended daily allowance of folate, B_{12}, and B_6.[2]

CLINICAL COMMENTARY

Folate for CAD an unanswered question

James M. Gill, MD, MPH

Christianacare Health System,Wilmington, Del

Folate seems like a simple, inexpensive, and relatively benign way to improve care. It is no wonder that many physicians have been recommending folate to their patients with CAD for years. However, as responsible physicians, we need more comprehensive evidence on the benefit of folate before making such universal recommendations.

Several points are important: first, most of the evidence on folate is from observational studies. Only 1 interventional study has shown benefit for patients with CAD, and this study used folate in combination with vitamins B_6 and B_{12}. Therefore, if physicians are going to recommend folate supplementation to their patients with CAD, they should recommend this combination rather than folate alone. Also, since this study only included patients who are post-PTCA, it may not apply to all patients with CAD. In short, there is still a fair amount of uncertainty in the answer to this clinical question. We should discuss this uncertainty with our patients, and come to a mutual decision based on preferences.

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