

CORNERSTONE Critiques

Commentary by Richard A. Johnson, MD, on Current Literature

Intervention Study Supports Homocysteine-Lowering Treatment to Slow Progression of Atherosclerosis

Effect of Homocysteine-Lowering Treatment with Folic Acid Plus Vitamin B₆ on Progression of Subclinical Atherosclerosis: A Randomised, Placebo-Controlled Trial

Vermeulen EGJ, Stehouwer CDA, Twisk JWR, et al. *Lancet*. 2000;355:517–522.

The possibility of reducing the risk of atherothrombotic disease by reducing homocysteine levels via vitamin supplementation is worthy of investigation. Recent studies have shown that high concentrations of homocysteine are associated with an increased risk of atherothrombotic disease and that elevated homocysteine levels can be reduced by treatment with folic acid and vitamin B₆. A Netherlands team led by Vermeulen conducted a randomized, placebo-controlled trial of homocysteine-lowering treatment in healthy siblings of patients with premature atherosclerotic disease. The 2-year trial was designed to determine the effects of supplementation with vitamin B₆ and folic acid on markers of subclinical atherosclerosis. A total of 158 healthy siblings of 167 patients with premature atherothrombotic disease (onset before the age of 56 years) agreed to participate in the trial. Eighty participants were randomized to daily placebo and 78 were randomized to daily supplementation with 5 mg folic acid and 250 mg vitamin B₆. Assessments were conducted at baseline, 1 year, and 2 years. At 2-year follow-up, 66 patients remained in the placebo

arm and 68 patients remained in the treatment arm. As compared with placebo, treatment with folic acid and vitamin B₆ was associated with a decrease in both fasting homocysteine level and postmethionine homocysteine levels. In the treatment group, fasting and postmethionine homocysteine levels decreased by 49.7% and 46.2%, respectively, compared with baseline; and by 38.3% and 30.6%, respectively, compared with placebo. At 2-year follow-up, 14 persons in the placebo group and 6 persons in the treatment group had a newly abnormal exercise electrocardiography test; vitamin supplementation was associated with a decreased risk of having an abnormal exercise test at follow-up. Vitamin treatment, however, was not associated with improved ankle-brachial index pressures or with improved peripheral arterial or carotid arterial outcomes. Vitamin treatment to lower homocysteine concentrations can slow the progression of atherosclerotic disease, conclude the authors. They suggest that trials with clinical endpoints should be undertaken to establish guidelines for homocysteine-lowering treatment in the management of atherothrombotic disease.

COMMENTARY

According to this randomized, placebo-controlled intervention trial, homocysteine may not only be a causative factor in the development of coronary artery disease (CAD), but there is also encouraging data that with aggressive treatment to lower plasma levels of homocysteine, the progression of atherosclerosis is slowed—as measured with the surrogate marker of an abnormal treadmill test. Study limitations that included a small sample size and the targeted population studied (siblings of those with premature CAD) could limit the generalizability of results. Nonetheless, the emerging evidence about the role of homocysteine is beginning to look much like the earlier data when total serum cholesterol was first suspected as an independent risk factor for CAD. The 5-mg dose of folic acid used in the treatment group is considerably higher than what most patients use as a supplement today, and should be noted as a feature of this study.

Exercise Improves Endothelial Function in CAD

Effect of Exercise on Coronary Endothelial Function in Patients with Coronary Artery Disease

Hambrecht R, Wolf A, Gielen S, et al. *N Engl J Med.* 2000;342:454–460.

Because coronary atherosclerosis is associated with progressive impairment of coronary endothelial function, the correction of endothelial dysfunction has been proposed as a therapy in coronary artery disease (CAD). Hambrecht and associates therefore undertook a study to determine whether exercise training in patients with CAD corrects endothelial dysfunction and improves coronary flow reserve. Nineteen men ≤ 70 years of age with documented, stable CAD were enrolled in the study. After baseline assessment, the patients were randomly assigned to an exercise training group or a physically inactive control group. The 10 patients in the exercise group underwent 4 weeks of vigorous exercise consisting of 6 daily supervised 10-minute exercise periods. The 9 patients in the control group maintained a sedentary lifestyle. No significant differences in baseline assessments were seen between the 2 groups. At 4-week follow-up assessment, significant differences between the 2 groups were seen in vasoconstrictive response to 3 doses of acetylcholine. In the exercise training group, the mean

vasoconstrictive response to the intermediate dose of acetylcholine ($0.72 \mu\text{g}/\text{min}$) and the highest dose of acetylcholine ($7.2 \mu\text{g}/\text{min}$) were significantly weaker compared with baseline; coronary artery constriction was reduced by 48% and 54%, respectively, at the 2 doses. Exercise training also conferred significant improvement in coronary blood flow velocity from baseline: 96%, 73%, and 73% at the low, intermediate, and high doses of acetylcholine, respectively. In addition, a 29% increase in coronary blood flow reserve as assessed by adenosine infusion was seen in the exercise training group, a significant improvement. According to the authors, exercise training improves the endothelium-dependent vasodilation of large coronary conduit and resistance vessels in patients with coronary atherosclerosis. The authors suggest that correction of endothelial dysfunction may in part explain the positive effects of regular exercise on myocardial perfusion; furthermore, they propose that endurance training may be a viable therapy for patients with stable CAD.

COMMENTARY

Hambrecht et al, in this randomized trial assessing endothelial response to biologic vasoconstrictors and vasodilators via catheter-delivered challenges, support an independent role for exercise as a factor in increasing vascular endothelial stability. Historically, it has been known that exercise improves a variety of known risk factors associated with CAD, but these collective improvements did not seem to sufficiently explain all the beneficial correlative data. A direct beneficial adaptive effect of exercise on vascular endothelium via biochemical mechanisms now seems evident. This knowledge may be much more helpful in motivating patients to exercise than vague admonitions that the patients will feel better or might lose weight if they don't overeat.

No Benefits in Cognitive or Functional Status Demonstrated by Estrogen in Treating Alzheimer's Disease

Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial

Mulnard RA, Cotman CW, Kawas C, et al. *JAMA*. 2000;283:1007–1015.

Estrogen replacement therapy (ERT) as a treatment for Alzheimer's disease (AD) in women has begun to receive broad-based support despite inadequate scientific confirmation of efficacy. Proof that estrogen enhances cognition and delays progression of dementia in women with AD rests only on the results of brief, nondefinitive trials with small numbers of patients. Mulnard and coworkers report on the largest and longest trial to date of ERT in the treatment of AD in women. One hundred twenty women with mild to moderate AD—as assessed by scores between 12 and 28 on the Mini-Mental State Examination (MMSE)—were recruited between October 1995 and January 1999 from 32 centers participating in the Alzheimer's Disease Cooperative Study. Women who had undergone hysterectomy were accepted into the study and were randomized to receive one of three 1-year treatment regimens: 0.625 mg/d estrogen (42 patients); 1.25 mg/d estrogen (39 patients); or placebo (39 patients). Assessment of global, cognitive, and functional measures were made at baseline and at 2, 6, 12, and

15 months of follow-up. At study end, the score on the main outcome measure, the Clinical Global Impression of Change (CGIC), was 5.1 in the combined estrogen group and 5.0 in the placebo group. This difference was not significant; nor were significant differences seen between the 2 groups in scores on either the MMSE or the Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog). A significant worsening of the patients in the estrogen group as compared with the placebo group was seen on the Clinical Dementia Rating Scale (CDRS), however. These trends were also apparent when a 3-group comparison was completed. Overall, worsening of AD was seen in 80% of the patients receiving estrogen and 74% of the patients taking placebo. The authors conclude that 1 year of ERT does not slow progression of mild to moderate AD in women, nor does it improve global, cognitive, or functional outcomes in these patients. Although the potential role of estrogen in preventing the onset of AD requires further research, the authors believe that ERT for the treatment of AD offers no benefit—and indeed may be detrimental.

COMMENTARY

Unfortunately, given the devastating social implication of this disease, physicians are advising patients to use ERT for the prevention of AD without sufficient science. This randomized, double-blind, placebo-controlled trial did not show any benefit in cognitive or functional status in women with mild to moderate AD who were treated for a 1-year period. The degradation in function in both the treatment and control groups was of significant magnitude, and the conclusion by the authors that ERT does not slow the rate of cognitive and functional decline in AD appears valid. As in other studies, the authors noted a short-term positive benefit on the MMSE in women treated with low-dose estrogen up to 2 months, but the effect was not sustained. Additionally, the authors indicated that this study does not address the potential beneficial role of ERT in delaying or preventing the onset of AD.