B Vitamins and Cardiovascular Disease

An abundance of research suggests a relationship between blood homocysteine levels and heart disease risk, as convincingly summarized in a 1995 meta-analysis of 28 studies. (Boushey, Beresford, et al., 1995) Homocysteine is produced in the body as a byproduct of the one-carbon cycle, which generates methyl groups for the synthesis of innumerable compounds essential to life and health, including DNA itself. Homocysteine normally gets recycled and does not accumulate to a large extent. The nutrients directly involved as cofactors that keep the one-carbon cycle operating efficiently include several of the B vitamins, notably folate, vitamin B-6 and vitamin B-12. When these B vitamins (and some other compounds) are present in adequate amounts, homocysteine is kept at a relatively low level in the body. A number of observational studies found that populations with low homocysteine levels had a lower incidence of heart disease than populations with higher levels of homocysteine.

A recent trial illustrates the importance of distinguishing between effects of B vitamins in people depending on their baseline level of homocysteine.

It was clearly demonstrated that giving extra amounts of the B vitamins lowered homocysteine levels, and so it seemed likely that such supplementation would reduce the risk of cardiovascular disease in the population as a whole. Some researchers urged public health authorities to endorse widespread supplementation with these B vitamins, without waiting for results from a number of controlled studies that were undertaken to test the hypothesis that reducing homocysteine levels would also reduce the risk of cardiovascular disease. (Stampfer & Malinow, 1995) Numerous clinical trials on B vitamins, homocysteine, and heart disease or stroke were undertaken, involving tens of thousands of patients in several countries. In general, the interventions were undertaken in groups of older patients who had just suffered an event such as a stroke or a myocardial infarction (MI). One can reasonably question whether such trials are true tests of prevention.

A recent trial illustrates the importance of distinguishing between effects in people depending on their baseline level of homocysteine. In a clinical trial involving 506 people without diabetes and with no cardiovascular disease, B vitamins or a placebo were given for a period of three years. The vitamin supplement provided five mg folic acid, 400 mcg vitamin B-12, and 50 mg vitamin B-6. In this group of people at low risk for cardiovascular disease, the high-dose B vitamin supplementation reduced progression of early-stage subclinical atherosclerosis in those with a baseline homocysteine level of 9.1 micromole per liter or greater, but not in those with lower homocysteine levels. (Hodis, Mack, et al., 2009)

It is uncertain whether the clinical trials have sufficient statistical power to detect an effect, if there is one. Observational studies and nonrandomized trials generally overpredict the magnitude of an effect by as much as 50 to 100 percent. (Meyskens & Szabo, 2005) "Because sample sizes for clinical trials are generally based on the relative risks (or the equivalent) shown in observational studies, there is a high likelihood that randomized trials are consistently underpowered, thereby missing a small, but real effect." (Meyskens & Szabo, 2005)

An analysis by a collaborative group of researchers involved in B vitamin trials concluded that the homocysteine trials, in particular, "may not involve

a sufficient number of vascular events or last long enough to have a good chance on their own to detect reliably plausible effects of homocysteine lowering on cardiovascular risk." (B-Vitamin Treatment Trialists' Collaboration, 2006) Other researchers have noted that the expected effect of the B vitamins on cardiovascular disease is in the range of 10 to 15 percent and the clinical trials were "generally underpowered" to detect such an effect. (Wald, Wald, et al., 2006) The latter group observed that, despite the problem of having low statistical power, reports from the studies "tend to inappropriately interpret non-significant effects as evidence of no effect."

KEY CLINICAL TRIALS

The VISP (Vitamin Intervention for Stroke Prevention) trial was undertaken in 3,680 patients who had already suffered a non-disabling stroke (cerebral infarction). (Toole, Malinow, et al., 2004) All of the patients "received best medical and surgical care plus a daily multivitamin containing recommended amounts of the non-study vitamins." The trial tested high-dose B vitamins or low-dose B vitamins as compared to placebo, over a 2-year period. The high-dose formula contained 25 mg pyridoxine (B-6), 400 mcg B-12, and 2500 mcg folic acid. The low-dose formula contained 200 mcg B-6, six mcg B-12, and 20 mcg folic acid. The high-dose formula lowered homocysteine more than the low-dose formula. Subjects with a lower homocysteine level at baseline were less likely to suffer another stroke, a coronary event, or death, but the supplementation had no effect on risk. However, the authors say that "further exploration of the hypothesis is warranted and longer trials in different populations with elevated total homocysteine may be necessary." (Toole, Malinow, et al., 2004)

Dr. David Spence and others involved in the VISP trial later published an analysis of the effects of the B vitamin supplements "in patients most likely to benefit from the treatment." (Spence, Bang, et al., 2005) For this analysis, they excluded people with very low or very high serum B-12 levels at baseline in order to exclude those with malabsorption and those already being treated with B-12. In the 2,155 patients considered in this analysis, there was a 21 percent reduction in the risk of stroke, coronary disease, or death in the high-dose B vitamin group. They suggest that, "in the era of folate fortification, B-12 plays a key role in vitamin therapy for total homocysteine. Higher doses of B-12 and other treatments to lower total homocysteine may be needed for some patients." (Spence, Bang, et al., 2005)

After other trials failed to find the benefits of B vitamins, Dr. Spence published an editorial entitled "Call Off the Funeral," urging researchers not to jump to the conclusion that B vitamins have no impact on cardiovascular disease without carefully evaluating the design of current trials, and especially whether studies are incorporating a sufficient amount of vitamin B-12. (Spence, 2006)

The Norwegian Vitamin trial (NORVIT) studied the effects of B vitamins in 3,749 men and women who were enrolled in the trial within seven days after suffering an MI. (Bonaa, Njolstad, et al., 2006) The patients were given 800 mcg of folic acid, 400 mcg of B-12, and 40 mg of B-6; or only the folic acid and B-12; or only the B-6; or a placebo. The primary endpoint was suffering another MI, a stroke, or sudden death due to coronary artery disease within a period of more than three years (40 months). Treatment with folic acid and B-12 lowered homocysteine but did not have a benefit on disease outcome. In the group given the relatively high dose of B-6, there was a trend toward increased risk, which the authors say "could readily be explained by chance."

The Heart Outcomes Prevention Evaluation (HOPE-2) trial involved 5,522 patients with vascular disease or diabetes who were given 2.5 mg of folic acid, 50 mg of B-6, and one mg of B-12, or who received a placebo for a period of about five years. (Lonn, Yusuf, et al., 2006) The average age of the patients at the beginning of the study was 69 years. The primary outcome measure was whether the subjects suffered an MI, a stroke, or death from cardiovascular causes. The B vitamin treatment reduced homocysteine levels but did not reduce the risk of major cardiovascular events. There were, however, fewer nonfatal strokes in the treatment group. More than 70 percent of the subjects lived in areas with mandatory folic acid fortification of food. The authors say, "This exposure probably reduced the number of patients with substantially increased homocysteine levels, the subgroup that might be most likely to benefit from B vitamin supplementation." (Lonn, Yusuf, et al., 2006)

As in other trials of patients who have suffered a stroke or MI, the subjects in the HOPE-2 trial were being given extensive medical care and were taking the medications indicated for their condition. For example, the B vitamin group used the medications shown below, among others. (Lonn, Yusuf, et al., 2006) It is reasonable to wonder whether a few B vitamins can realistically be expected to make an impact above and beyond the effects of standard medical care in such patients.

PERCENTAGE OF HOPE-2 SUBJECTS (IN B VITAMIN GROUP) TAKING THE FOLLOWING MEDICATIONS

MEDICATION	PERCENT USING
Aspirin or antiplatelet agents	78%
Beta-blockers	46%
Lipid-lowering drugs	59%
ACE inhibitors	66%

The WAFACS trial was a test of the effect of B vitamins on cardiovascular disease (CVD) in 5,442 women who were U.S. health professionals with a history of CVD or three or more coronary risk factors. Subjects were given a placebo or a B vitamin supplement containing 2.5 mg folic acid, 50 mg vitamin B-6, and one mg vitamin B-12 for a period of just over seven years. Homocysteine levels were reduced, but there was no impact on cardiovascular events. (Albert, Cook, et al., 2008)

The VITATOPS (Vitamins to Prevent Stroke) trial recruited more than 8,000 patients with recent stroke or TIA (transient ischemic attack) to test B vitamin therapy consisting of two mg folic acid, 25 mg B-6, and 500 mcg B-12 in an effort to determine whether the supplements plus "best medical and surgical management" would reduce the combined incidence of stroke, MI, and vascular death over a period of two years. Patients were recruited from 104 medical centers in 20 countries on five continents. (Hankey, Algra, et al., 2007) Results reported in 2010 indicated no significant risk reduction from the B vitamin treatment. (VITATOPS Trial Study Group, 2010)

Bottom Line

There is clear evidence that, in the general population, people with lower homocysteine levels have a lower risk of cardiovascular disease. It is known that giving B vitamins will lower homocysteine levels if they are high, and it was reasoned that lowering these levels would also lower heart disease risk in the population. Has this hypothesis been fairly tested in the clinical trials? Interventions in older people with recent cardiovascular events may not be the appropriate test for evaluating the effect of lowering homocysteine levels on the risk of cardiovascular disease in the general population.

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