Homocyst(e)ine[1] and Cardiovascular Disease

June 6, 2000

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Homocyst(e)ine is an amino acid made by the body during normal metabolism. An elevated blood level of homocyst(e)ine has been associated with atherosclerotic vascular disease (blockages of the arteries in the heart, brain and/or lower limbs) and venous thrombosis. Although the pathogenic mechanisms at work have not been defined, experimental evidence suggests that homocyst(e)ine damages the inner lining of the artery, and promotes thrombosis, possibly affecting blood coagulation.

There are many determinants for blood homocyst(e)ine levels. Normal homocyst(e)ine metabolism is partly controlled by vitamins B_6, B_{12} and folic acid in the diet. Even sub-clinical deficiencies of these vitamins, which may result from inadequate intake from the diet or the inability of the body to absorb these vitamins, can lead to an elevated homocyst(e)ine level. Other factors increasing homocyst(e)ine include age, sex (higher in males), genetic predisposition and kidney function.

In the past 10 years, there has been substantial epidemiologic evidence for an association between homocyst(e)ine and the risk of developing heart attacks, strokes and thrombosis. These data, however, are not consistent across all studies. Experts continue to debate discrepancies between studies. However, the totality of evidence would suggest that elevated homocyst(e)ine is an independent risk factor for the development of atherosclerosis. The risk associated with high homocyst(e)ine levels is said to be similar to the cardiovascular risks posed by high cholesterol, smoking and hypertension.

The method of treating elevated homocyst(e)ine levels remains a matter of controversy. While folate therapy alone is sufficient to correct elevated plasma homocyst(e)ine levels in most patients, sub-clinical deficiencies of vitamin B12 or B6 may be left untreated, especially in older patients. For these reasons, some physicians prefer a combination of folate, B12 and B6. Although the amounts required are generally in excess of the current recommended daily intakes, there is little known risk to the patient. A high intake of folic acid may, however, mask the symptoms of vitamin B12 deficiency and pernicious anemia and may precipitate or exacerbate the neurological consequences of these conditions.

Supplementation has also been proven effective in improving endothelial function and possibly causes the regression of carotid plaque. It is, however, not known whether supplementation can reduce the risk of vascular disease or reduce the risk of recurrence in patients who already have the disease. Some small-scale studies suggest a beneficial effect of B-vitamin supplementation on the development of vascular disease. At least 10 large-scale trials of vitamin supplementation to reduce homocyst(e)ine for the prevention of heart disease and stroke are currently underway. Until the results of these studies are available, we acknowledge that there is limited evidence that treatment of elevated homocyst(e)ine can prevent the development of vascular disease, or prevent recurrence of cardiovascular disease events.

Currently, some experts recommend the measurement of homocyst(e)ine (and if necessary treatment with vitamin supplementation to reduce homocyst(e)ine levels) for patients with vascular disease (heart disease, stroke or thrombosis), a family history of premature atherosclerotic disease or for patients who lack traditional risk factors. At this point, the data on the effectiveness of supplementation for the improvement of cardiovascular health does not provide enough support to recommend routine testing of homocyst(e)ine levels in healthy people.

Presently, the absence of clinical trial evidence precludes a recommendation for a level of supplementation or general intake of folic acid, B6 or B12 for the prevention of cardiovascular events. We do not recommend routine testing of homocyst(e)ine levels in healthy people at this time. On the other hand, diet counseling to increase the intake of these vitamins from foods may be recommended for those with high homocyst(e)ine levels. The evidence is strong that women who are planning a pregnancy, or who are likely to become pregnant, can reduce the risk of neural tube defects in their offspring by taking a daily supplement containing 0.4 mg of folic acid prior to, and in the early stages of, their pregnancy. Further information on this topic is available in the 1999 Health Canada publication entitled "Nutrition for a Healthy Pregnancy".

For good cardiovascular health, we continue to stress the importance of following a healthy, balanced diet in accordance with "Canada's Food Guide to Health Eating". The Food Guide recommends 5-10 servings of vegetables and fruits per day, 5-12 servings of cereal products per day (preferably whole grain and enriched cereal products) and the consumption of legumes (e.g., dried peas, beans and lentils). These basic dietary practices will also help to ensure a high dietary folate intake.

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1. "What constitutes the risk factor, and what is measured, is the combination of homocysteine, homocystine and mixed cysteine-homocysteine disulfide; this is called total homocysteine and spelled homocyst(e)ine". (from: Mudd SH, Levy HL. Plasma homocyst(e)ine or homocysteine? *N Engl J Med* 1995;333:325).