Homocysteine: To screen and treat or to wait and see?

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Novel risk factors for cardiovascular diseases, including infectious agents such as *Chlamydia pneumoniae* and *Helicobacter pylori*, inflammatory mediators such as C-reactive protein and interleukin-6, and hemostatic markers, are being uncovered at a rapid pace. A high homocysteine level is one of the most recent risk factors to be identified. The measurement of total plasma (or serum) homocysteine (tHcy) represents the sum of oxidized (as homocysteine or the homocysteine–cysteine mixed disulfide) and protein-bound homocysteine. Despite extensive research the mechanisms by which homocysteine causes arterial damage are not fully understood. Homocysteine contains a reactive sulfydryl group than can react with plasma constituents, and this may promote oxidative damage and induce the oxidation of low-density lipoprotein. An elevated homocysteine level induces thrombogenicity, causes a procoagulant state and promotes the proliferation of smooth muscle cells.

The epidemiological data linking tHcy to atherosclerosis is extensive in case–control studies, but the strength of this association is weaker in prospective studies. Thus, the causal relationship between tHcy and heart disease is not as strong as one would like to make recommendations regarding screening and treatment for the prevention of cardiovascular diseases.

tHcy levels are associated with sex (i.e., levels are higher in men), postmenopausal status in women, increasing age, nutritional intake (and plasma levels) of vitamins B_{12}, B_6 and folate, renal function, genetic predisposition and thyroid function.[1] Some medications, such as niacin, methotrexate and fenofibrate, can also cause elevated tHcy levels.[1,2]

Because tHcy level is a continuous biochemical variable, normality is difficult to define. Hyperhomocysteinemia is usually defined as a tHcy level in the 90th or 95th percentile of a control population; in most studies, this is approximately 15 μmol/L. In high risk patients this may be too high and some experts recommend a level of 10 μmol/L as a therapeutic target;[3,4] others are more conservative.[5] The treatment of elevated tHcy is relatively simple. Vitamin supplementation, starting with folate (0.4–5 mg/day) and adding vitamin B_6 (25–50 mg) and B_{12} (0.5–1.0 mg) is highly effective in lowering levels.

The enthusiasm of patients to embrace novel and "natural" treatments is, well, natural. We have learned, however, that vitamin supplementation may not be useful,[6,7] and when taken in very large doses may potentially be harmful.

So where do things stand with homocysteine? Should we bother to screen and treat elevated homocysteine levels? At present, there are 3 approaches:

- don't test and don't treat
- treat everyone because it makes sense and treatment is cheap
- consider screening patients with established atherosclerotic disease and initiating treatment if the tHcy level is above 10 μmol/L

There are currently at least a dozen large-scale studies being conducted in the United States, Canada and Europe (especially in the Scandinavian countries) to examine the effects of lowering tHcy on cardiovascular morbidity and mortality.[8] Roughly 45 000 patients are currently enrolled in trials on the effects of vitamin supplementation on cardiac events and 15 000 more in trials on stroke prevention. In Canada the HOPE-TOO trial will follow the path of the HOPE trial[7,8] and attempt to identify the role of vitamin supplementation in cardiovascular disease prevention.

In the interim Drs. Booth and Wang, with the Canadian Task Force on Preventive Health Care,[9] review the information available to date (see page 21) and advise that caution is warranted in extrapolating directly from imperfect epidemiological data. The American Heart Association,[3] the International Task Force on the Prevention of Coronary Artery Disease,[5] the Canadian Cardiovascular Society[4] and the Heart and Stroke Foundation of Canada agree that we must wait for the results of ongoing clinical studies before making any change to public health policy. We must also encourage those conducting clinical studies to study the potential benefits of lowering plasma tHcy levels in the prevention of cardiovascular diseases. Clinical trialists have the day ... and the last say.

In the absence of definitive evidence it might be best to work hard at collecting the data and exercise caution in our endorsement of therapies that appear to make sense. In the meantime, a healthy diet rich in legumes, orange juice and green leafy vegetables is a recommendation that has withstood the test of time. The dilemma lies in the treatment of moderately severe hyperhomocysteinemia, once identified. We know diet alone is insufficient to normalize tHcy levels. Until the data are in, physicians must use their best judgement. Our enthusiasm for the potential of novel preventive strategies should not diminish our diligence in

implementing simple health measures and prescribing treatments proven to effectively reduce the risk for cardiovascular diseases.

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