

## UPDATE ON FOLIC ACID SUPPLEMENTATION

A marker for heart disease is homocysteine, an amino acid believed to be involved in the development and progression of atherosclerosis. Indeed, patients with high homocysteine levels, above 10  $\mu\text{mol/L}$ , have an increased risk of cardiovascular disease. Risks double between 10  $\mu\text{mol/L}$  to 15  $\mu\text{mol/L}$ , and will double again from 15  $\mu\text{mol/L}$  to 20  $\mu\text{mol/L}$ . High homocysteine levels are definitely a marker for vascular disease. Most clinical trials in this area, however, are based on observational data. Due to popular press, many of my patients are demanding their homocysteine levels be measured and treated. Let us look at the evidence for lowering homocysteine values.

### Lowering Blood Homocysteine with Folic Acid Supplements

Folic acid, at 0.5 mg to 5 mg on average a day, reduces homocysteine levels by 25%, according to a meta-analysis of randomized controlled trials (95% confidence interval,

23% to 28%;  $P < .001$ ).<sup>1</sup> These trials assessed the effects of folic acid based supplements on blood homocysteine concentrations. Results showed vitamin B<sub>12</sub> (average dose 0.5 mg daily) produced an additional 7% reduction in blood homocysteine levels.<sup>1</sup> Vitamin B<sub>6</sub> did not have a significant additional effect. The recommendation of this meta-analysis demonstrated that folic acid, 0.5 to 5 mg a day, and 0.5 mg of vitamin B<sub>12</sub> should reduce blood homocysteine concentrations by a quarter to a third.<sup>1</sup>

Multivariate regression analysis was used to determine the effects of different doses of folic acid on homocysteine concentrations. Individual data was collected on 1,114 people included in 12 trials.

### Folate Treatment:

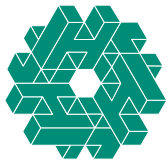
#### Lower Restenosis Rate after Angioplasty

Elevated levels of plasma homocysteine are associated with a higher rate of restenosis,

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according to a study on the decreased rate of coronary restenosis after lowering of plasma homocysteine levels. In the first major randomized control trial with the supplementation of folate, vitamin B<sub>12</sub> and vitamin B<sub>6</sub> demonstrated marked benefit in reducing restenosis following balloon angioplasty.<sup>2</sup>

A total of 205 patients were randomly selected and divided into two groups for a period of six months: patients on a combination of folic acid (1 mg/day), vitamin B<sub>12</sub> (400 mcg/day) and vitamin B<sub>6</sub> (10 mg/day); and another patient group on placebo (matching doses). Patients selected had successful angioplasty.

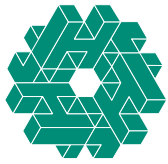
Results from the trial showed that the vitamin cocktail reduced mean homocysteine levels from 11.1 +/- 4.3 µmol/L at baseline to 7.2 +/- 2.4 µmol/L at six months (P < .001).<sup>2</sup> Only patients with a reduction in serum homocysteine values demonstrated a benefit. The primary end point at six months was restenosis, as assessed by quantitative coronary angiography. In this case, 19.6% of patients in the vitamin cocktail demonstrated a lower rate of restenosis versus 37.6% of patients on placebo (P = .001). A secondary end point was a composite of major adverse cardiac events. The need for revascularization of the target lesion was approximately cut in half by folate supplementation (10.8% versus 22.3%, P = .047).<sup>2</sup>

## Physician's Perspective

*Unfortunately, only one small, randomized clinical trial has demonstrated that lowering homocysteine levels decreases cardiovascular risk in patients undergoing angioplasty. Ongoing clinical trials in the next number of years will answer this question more broadly and definitively. We need much more data before we can feel confident in recommending folic acid reducing regimens in patients at a high risk for vascular disease. Many times we*

*have been fooled by observational data and small clinical trials with inadequate power. In the past, radical mastectomies were recommended for women with breast cancer. The evidence demonstrated that a modified and simpler procedure had the same effect. Premature ventricular contraction (PVC) suppression suppressed life. The lipid effect of hormone replacement therapy did not translate to a cardiovascular protective effect. Vitamin E, an antioxidant, was not shown to be cardiovascular protective in over 50,000 patients in randomized controlled trials for heart disease prevention. Beta-carotene was found to be harmful and, in fact, promoted cancer, specifically in smokers. One must realize that observational data is purely that. One can never adjust adequately for biases introduced in this type of data. We have been burned many times. A doubling of risk in observational data is insufficient to recommend therapy. It should raise eyebrows and encourage proper research. However, if the observational data suggest a greater than five-fold increase risk, such as cigarettes and lung cancer, then the data become much more convincing.*


*The measurement of homocysteine should be done in research projects and in patients whose atherosclerosis rate of progression cannot be explained by conventional risk factors. The trial presented thus far is too small to influence clinical practice. The average Canadian has a number of cardiac risk factors that should not be ignored. We have only controlled 16% of hypertensives in Canada. Most patients started on cholesterol-lowering medication, yet do not maintain the drug long term. Canadians are gaining weight. We are becoming more obese and, for at least 50% of us, overweight is affecting our health. The average Canadian consumes 37% of calories*



*from fat. We have many proven risk factors, yet patients are undertreated. Many of my patients want to take folic acid and vitamin B<sub>12</sub>. They are better off modifying conventional risk factors, which are of proven value.*

*A second perspective can be considered. The small randomized controlled trial demonstrates close to a 50% reduction in restenosis with a simple and inexpensive therapy. Prescribing folic acid at 1 mg a day with or without vitamin B<sub>6</sub> leads to fewer repeat angioplasty to the target lesion and will become my standard practice until further information is available. Remember, our patients should not forget other proven risk*

*factor modification as discussed above. It is important to note, myocardial infarction, strokes or mortality were not altered. The final answers await future research.*

*The bottom line is — we need more data.* 

#### References

1. Homocysteine Lowering Trialists' Collaboration. Lowering blood homocysteine with folic acid based supplements: Meta-analysis of randomized trials. *BMJ* 1998; 316(7135):894-98.
2. Schnyder G, Roffi M, Pin R, et al: Decreased rate of coronary restenosis after lowering plasma homocysteine levels. *N Engl J Med* 2001; 345(22):1593-600.

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