Reducing Coronary Artery Disease by Decreasing Homocysteine Levels

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Age-adjusted rates of deaths due to cardiovascular disease have declined by more than 50% in the past 25 years among whites and blacks of both sexes. This decrease is due, in part, to improved treatment at the acute care level and to effective primary prevention, such as reducing plasma levels of lipids; smoking cessation; and controlling blood pressure, blood glucose levels in patients with diabetes, and weight. As important as established risk factors are, many patients who have a myocardial infarction have normal cholesterol levels and no other known risk factors. An elevated plasma level of homocysteine correlates with an increased risk for coronary artery disease (CAD) and is an important measurable biomarker. An increase in plasma concentration of total homocysteine, hyperhomocysteinemia, is an important independent risk factor for vascular disease.

**Literature Review**

The results of more than 75 clinical and epidemiological studies have indicated a positive correlation between total homocysteine levels and CAD, peripheral arterial disease, stroke, and venous thrombus. Many also indicated a positive correlation between use of vitamin supplements provided via enriched cereal and a subsequent decrease in homocysteine levels, and hence CAD.

**Coronary Artery Disease and Homocysteine**

Homocysteine is a toxic, nonproteinogenic, sulfur-containing, highly reactive amino acid that is synthesized during protein catabolism by the conversion of methionine to cysteine. Homocysteine is metabolized by transsulfuration, which depends on vitamin B₆, and remethylation, which relies on folate and vitamin B₁₂. Early studies...
revealed a strong, nonlinear, inverse relationship between plasma levels of folate and total homocysteine. Results of the Framingham Heart Study indicated that folate, vitamin B_6_, and vitamin B_12_ play significant roles in the metabolism of homocysteine in elderly patients.^{5,10} Weaker inverse relationships also exist between plasma levels of vitamin B_12_ and vitamin B_6_ and between intake of folate and vitamin B_6_. In these earlier studies, elevated homocysteine levels were defined and the doses of each of the vitamins given were reported. Recommendations were made for interventional studies to determine if decreasing total homocysteine levels would lower the prevalence of CAD^{12} (see Table).

A meta-analysis of 27 studies relating homocysteine levels to CAD and 11 studies of the effects of folic acid on total homocysteine levels suggested that an increase of 5 µmol/L in the level of total homocysteine (normal level, 5-15 µmol/L)^{12} increased the risk for CAD as much as an increase of 0.52 mmol/L (20 mg/dL) in the level of plasma cholesterol does.^{12} The conclusion was that intake of larger amounts of folic acid was associated with a decrease in the prevalence of CAD. In a review published in 1996, Mayer et al^{15} reported that homocysteine was gaining recognition as a risk factor for CAD. They found that elevated homocysteine levels were an independent risk factor for cardiovascular disease, similar to smoking and increased levels of cholesterol.

In the European Concerted Action Project, a large case-control study of 750 patients and 800 control subjects in 19 centers located in 9 different countries, levels of folate, vitamin B_6_, and vitamin B_12_, all of which modulate homocysteine metabolism, were inversely related to total homocysteine levels.^{15} Compared with nonusers of vitamin supplements, the subjects who took supplements had a substantially lower risk of vascular disease, a proportion of which was attributable to lower plasma levels of homocysteine.

At elevated levels, homocysteine can block production of nitric oxide in the endothelial cells in the walls of blood vessels, making the vessels less pliable and allowing plaque to build up.^{7} Several different mechanism have been proposed to explain the association between homocysteine levels and atherosclerotic vascular disease, including endothelial cell dysfunction or injury, promotion of the proliferation of smooth muscle cells into the intima, enhanced platelet aggregation, increased binding of lipoprotein(a) to fibrin, generation of free radicals, stimulation of oxidation of low-density lipoprotein, and procoagulant effects^{6,7,16,17} (see Figure). In a prospective study of the relationship between plasma levels of total homocysteine and mortality in 587 patients with angiographically confirmed CAD, Nygard et al^{6} concluded that the plasma level of total homocysteine was the strongest modifiable predictor of overall morbidity and mortality due to cardiovascular causes.

### Vitamin Supplementation

Woo et al^{2} measured the diameter of the brachial artery in 28 Chinese men and women 40 to 70 years old. The diameter was significantly lower (P < 0.05) in the 14 subjects with high homocysteine levels (>15 µmol/L) than in the 14 subjects with lower levels. The authors concluded that homocysteine level might be an independent risk factor for arterial endothelial function in healthy middle-aged adults. They also concluded that because endothelial dysfunction^{2,16} is a key early event in atherogenesis and is important in the dynamic behavior of plaque in the coronary circulation, these findings might have important pathophysiological and clinical implications.

In a study published in 1998, Refsum et al^{19} reviewed the results of 80 clinical and epidemiological studies on CAD that included more than 10 000 patients. The authors found that an elevated level of total homocysteine was a prevalent and strong risk factor for CAD and for arterial and venous thromboembolism. Homocysteine is independent of, but may enhance the effect of, the conventional risk factors, and seems to be a particularly strong predictor of mortality due to cardiovascular events. Refsum et al concluded that supplementation with B vitamins, in particular, folic acid, is an efficient, safe, and inexpensive means to reduce elevated levels of total homocysteine.

In a pivotal study, Malinow et al^{7} used cereal fortified with folic acid as a vehicle to deliver vitamins to determine whether vitamin supplementation altered the plasma levels of total homocysteine. They found that levels of total homocysteine decreased with increasing levels of folate. Total homocysteine levels greater than 15 µmol/L correlated with a 13% prevalence of coronary heart disease, 35% prevalence of strokes and 47% prevalence of peripheral vascular disease. On the basis of these results, Malinow et al estimated that an increase of 350 mg of folate in men and of 280 mg in women per day might prevent 49 500
deaths per year due to CAD. The cost of such a program must be weighed against the potential savings due to disease prevention.

In a study of patients with thyroid disease, plasma concentrations of total homocysteine were higher in patients with hypothyroidism than in patients with hyperthyroidism and control subjects. Total homocysteine levels in patients with hyperthyroidism did not differ significantly from those of control subjects. Serum levels of cholesterol and blood pressure were also elevated in the patients who had hypothyroidism. Building on this study, Hussein et al found that returning patients with hypothyroidism to a euthyroid state via thyroid hormone replacement therapy

<table>
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<td>Giles et al* (2000)</td>
<td>3173 subjects examined; 259 met inclusion criteria</td>
<td>Retrospective, controlled for confounding variables</td>
<td>Homocysteine level; nonfatal myocardial infarction; folate, vitamin B6, vitamin B12 levels; race, ethnicity; sex; age; hypertension; cholesterol level; diabetes; tobacco use</td>
<td>Estimate that 10% of all Americans have homocysteine levels &gt;15 µmol/L and are 2 times more likely than persons with lower levels to have a nonfatal myocardial infarction</td>
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<td>Mann* (2000)</td>
<td>n = 65</td>
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<td>Changing diet did not change vitamin levels Pills and cereal increased vitamin levels and decreased homocysteine levels Cereal worked best</td>
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<td>n = 56</td>
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<tr>
<td>Nygard et al* (1997)</td>
<td>n = 587 Men and women with angiographically confirmed coronary artery disease</td>
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<tr>
<td>Malinow et al** (1998)</td>
<td>n = 75 Primary care patients with established heart disease</td>
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<td>Levels of thyroid-stimulating hormone and homocysteine</td>
<td>An increase of 350 µg of folate per day for men and 280 µg for women could prevent 49 500 deaths per year due to coronary artery disease in the United States</td>
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caused a reduction in homocysteine levels in most instances. They recommended measuring levels of thyroid-stimulating hormone in patients with unexplained hyperhomocysteinemia because hypothyroidism is a treatable condition.20

Clinical Trials

In a review of research on homocysteine, Welch and Loscalzo5 predicted that randomized clinical trials would be necessary to determine the clinical efficacy of increasing folate levels to decrease levels of total homocysteine to yield an overall decrease in mortality due to cardiovascular disease. The authors defined the standard for homocysteine levels and reported that levels of total homocysteine greater than 15 µmol/L correlated most strongly with death due to CAD. In a review of biochemical biomarkers used to predict risk for cardiovascular disease, Pahor et al1 concluded that a better definition of the cardiovascular risk profile would help target primary and secondary prevention of CAD.

In a meta-analysis of data from the Third National Health and Nutrition Examination Survey, Giles et al4 found that elevated levels of total homocysteine correlated with lower plasma levels of vitamin B12 and folate in patients who had non-fatal myocardial infarction and that the likelihood of myocardial infarction was 2 times greater when levels of total homocysteine were greater than 15 µmol/L. Data from the survey included information on race, ethnic background, age, sex, education, hypertension, cholesterol levels, diabetes, and tobacco use, and the subjects were representative of the population distribution for the United States. Giles et al established that independent of race or ethnicity and when other factors are controlled for, 10% of Americans with levels of total homocysteine greater than 15 µmol/L are twice as likely as persons with lower levels to have a nonfatal myocardial infarction. This study was useful because it helped confirm baseline values for total homocysteine levels, described measurement techniques, considered race and ethnicity as confounding factors, and provided findings.

Men and women referred to a large, preventive cardiology clinic were used to determine whether patients with high levels of both lipoprotein(a) and total homocysteine were at increased risk for CAD compared with patients with only one or neither risk factor.21 Patients without known CAD referred to the clinic for evaluation for various reasons were used as a control group. Cross-sectional analysis established that lipoprotein(a) and total homocysteine interacted to increase the risk of CAD in women ($P=.03$). This finding was consistent with the findings of most of the retrospective case control studies reviewed but contradictory to those of previous prospective studies. In men, the effects of high levels of homocysteine alone, the effects of high levels of lipoprotein(a) alone, and the effects of both risk factors together diminished as the men got older. This finding was consistent with the findings of similar studies. The conclusion and study results support the hypothesis that total homocysteine and lipoprotein(a) interact to increase the risk of CAD. This study has important implications for the prevention and treatment of CAD in certain high-risk populations.

Critically Ill Patients

Critically ill patients are at high risk for high levels of total homocysteine.13 In a prospective study13 in 3 medical intensive care units serving both medical and surgical patients, hyperhomocysteinemia (total homocysteine >15 µmol/L) was more prevalent in critically ill patients...
In a recent pivotal study, dietary changes, vitamin supplements, and fortified cereals were used to increase intake of vitamins B6 and B12 to reduce total homocysteine levels. The effects of various sources of folate in the diet on total homocysteine levels were examined. Although no significant relationship was found between increasing dietary folate via food and decreases in the levels of total homocysteine, a significant relationship was found between using vitamin-enriched cereal or vitamin supplements and lower total homocysteine levels.

Remarkably consistent findings in more than 100 case-controlled and cross-sectional studies of more than 12,000 subjects indicate that patients with CAD tend to have higher blood levels of total homocysteine.

### Nursing Implications

An understanding of the implications of the physiological and pathophysiological consequences of homocysteine levels provides a new way of assessing patients’ risk factors and adds a new component to discharge teaching. Determining if a patient has the standard risk factors for heart disease does not provide a complete assessment in patients at risk for CAD. Nonstandard risk factors such as elevated levels of total homocysteine are more important in patients without the standard risk factors who have acute cardiac events. Elevated levels of total homocysteine interfere with hemostasis, activate the inflammatory response, and promote proliferation of smooth muscle cells. Elevated total homocysteine has an increased role in CAD, peripheral arterial disease, stroke, and venous thrombosis. Decreasing the plasma levels of total homocysteine can enhance endothelial function, a situation that is key in decreasing future cardiac events as well as cerebral vascular accidents.

Levels of homocysteine greater than 15 µmol/L are predictive of increased mortality and morbidity. A scientific advisory from the American Heart Association on homocysteine, diet, and cardiovascular disease recommends screening for total homocysteine in high-risk patients with a personal or family history of premature cardiovascular disease. The laboratory cost of determining the fasting plasma level of total homocysteine is approximately $40 to $80, depending on the laboratory, and may be covered by health-care insurance. The levels of total homocysteine should be measured in patients at high risk for heart disease, such as those who have a strong family history of coronary disease or who have angina.

Nursing interventions should focus on ways to lower total homocysteine levels. Critical care nurses can elaborate on the standard risk factors and can help patients understand the correlation between increased levels of total homocysteine and vascular disease. Discharge education should emphasize the importance of nutrition in reducing total homocysteine levels. Using vitamin-enriched cereal has been the most effective method of reducing total homocysteine levels, and hence CAD. Education should include the benefits of eating vitamin-enriched or fortified ready-to-eat cereal that contains 100% of the recommended daily allowance of folic acid (folate), pyridoxine hydrochloride (vitamin B6), and cyanocobalamin (vitamin B12). Patients can also be encouraged to increase consumption of foods rich in folate, vitamin B6, and vitamin B12, such as vegetables, fruits, legumes, meats, fish, and fortified grains and cereals. If diet alone does reduce the level of total homocysteine, patients with cardiac disease may benefit from supplemental multivitamins that contain 0.4 mg of folic acid, 2 mg of pyridoxine hydrochloride, and 6 µg of cyanocobalamin. Patients in primary care who have no evidence of cardiovascular disease but have levels of total homocysteine greater than 15 µmol/L could decrease their risk for CAD at least 2-fold by using vitamin supplementation to decrease their levels of total homocysteine.

### Acknowledgments

We gratefully acknowledge the technical assistance of Georgia Grant and Toni Pierce in preparation of this article.

### References


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Crit Care Nurse 2003;23 25-30
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