Dafna Rippel, MD, MAH, Andrew P. Ignaszewski, MD, FRCPC, Jiri J. Frohlich, MD, FRCPC

Lack of benefit in treating high homocysteine levels with vitamins

Recent studies suggest that most patients at risk of cardiovascular disease will not be helped by homocysteine-lowering treatment with folic acid, B_6, and B_{12}.

ABSTRACT: Homocysteine-lowering vitamin therapy has been widely prescribed in the belief that it will reduce cardiovascular events. While epidemiological studies have indicated a strong association between high plasma homocysteine levels and risk of cardiovascular disease, several recent prospective trials of homocysteine lowering with folic acid, vitamin B_6, and vitamin B_{12} have failed to show any benefit in patients with established cardiovascular disease. Three recent prospective randomized trials (VISP, NORVIT, and HOPE 2) suggest that measurement of homocysteine is not required for the management of most patients and that treating moderate hyperhomocysteinemia with vitamins does not reduce cardiovascular events.

In 1969, McCully suggested that elevated levels of plasma homocysteine (Hcy) are associated with atherosclerosis.[1] He noted high prevalence of hyperhomocysteinemia in patients with coronary artery disease (CAD) when compared with the general population. A number of other observations linking homocysteine with CAD followed.[2,3] A meta-analysis in 1995 by Boushey and colleagues suggested that for each 5 μmol/L increase in homocysteine there was a 70% higher risk of CAD, a 50% increase in cerebral vascular disease, and a strong association with peripheral vascular disease.[4] Based on these data, the authors suggested that 10% of the population's CAD risk is attributable to homocysteine. Another meta-analysis done by Eikelboom and colleagues confirmed these data, namely that "there is a strong dose-dependent positive association between plasma homocysteine levels and risk for cardiovascular disease" that "is independent of other known risk factors."[5] While these and other studies revealed a strong epidemiological correlation, they also emphasized the need for randomized clinical trials to establish causation.[6,7]

The first doubts about the causal role of homocysteine were expressed after the reported lack of association between CAD and a specific genetic polymorphism affecting *MTHFR* (677C→T).[8,9] Normally it would be expected that if a particular substance in blood causes a disease and its level is related to a genetic polymorphism, then that polymorphism would also be related to the disease.

While enzyme deficiencies caused by mutations in the *CBS* gene and the *MTHFR* gene are related to very high levels of homocysteine with vascular consequences,[9] a number of other causes of hyperhomocysteinemia (see Table 1) are known to be proven risk factors for vascular disease, and it is difficult to separate the effect of these factors from the specific consequences of hyperhomocysteinemia. In addition, blood sample handling, such as inadequate chilling, can also increase plasma homocysteine levels.

Dr Rippel is a clinical trainee in the Healthy Heart Program at St Paul's Hospital, Vancouver, BC. Dr Ignaszewski is head of the Division of Cardiology at St. Paul's Hospital and medical director of the Healthy Heart Program. Dr Frohlich is academic director of the Healthy Heart Program, director of the St. Paul's Lipid Clinic, and a professor of pathology and laboratory medicine at the University of British Columbia.

Three recent clinical trials

Three large prospective trials using vitamin therapy in high-risk populations were conducted over the last several years (see Table 2).

Vitamin Intervention for Stroke Prevention (VISP).[10] The aim of this trial was to determine whether the best medical and surgical management, risk-factor modification, and high-dose multivitamin therapy would reduce the incidence of recurrent cerebral infarction, coronary artery disease, or death in patients with a nondisabling cerebral infarction and fasting total homocysteine levels greater than the 25th percentile for North American stroke patients. A total of 3680 stroke patients were followed for 2 years on average. Although the Hcy

Table 1. Causes of elevated homocysteine levels.

Chronic medical disorders and conditions	Diabetes, rheumatoid arthritis, systemic lupus erythematosas, renal failure, malignant neoplasms and leukemia, hyperproliferative disorders, severe psoriasis, hypothyroidism, acute-phase response to illness, cardiac and renal transplantation
Drugs	Sex hormones, l-DOPA, isoniazid, some anticonvulsant agents (phenytoin, carbamazepine), cholesterol-lowering agents (cholestyramine, colestipol, nicotinic acid), metformin, thiazide diuretics, cyclosporine, folate antagonists (methotrexate), vitamin B_{12} antagonists (nitrous oxide), vitamin B_6 antagonists
Lifestyle factors	Tobacco use, physical inactivity, obesity, stress
Dietary factors	High alcohol and coffee intake, folate, vitamin B_6, and vitamin B_{12} deficiencies; increased methionine consumption
Demographic characteristics	Increasing age, male gender, postmenopausal state

Table 2. Main data and results of VISP, NORVIT, and HOPE 2 trials.

	VISP[10]	NORVIT[11]	HOPE 2[12]
Participants	3680	3749	5522
Follow-up (mean, in months)	24	36	60
Entry criteria	• Nondisabling ischemic cerebral infarct ⩽ 120 days • Hcy ⩾ 25th percentile*	<7 days from MI	Vascular disease / diabetes plus one other risk factor
Age (years)	>35 mean 66	30–85 mean 63	>55 mean 69
Homocysteine reduction	18%	27%	18%–20%
Primary endpoints (relative risk reduction compared to placebo)	1.00†	1.14‡ 1.22§ 1.08‖	0.95
MI (RRR compared to placebo)	0.90†	1.17‡ 1.23§ 1.06‖	0.98
Ischemic stroke (RRR compared to placebo)	1.00†	0.83‡ 0.81§ 1.02‖	0.75
Death (RRR compared to placebo)	0.90†	Total 1.19‡ 1.21§	• CV death 0.96 • Total death 0.98

* For North American stroke patient population
† High-dose vs low-dose vitamin therapy
‡ B_6 vs no B_6
§ Folic acid and B vitamin in combination vs placebo
‖ Folic acid and B_{12} vs no folic acid and no B_{12}

Table 3. Vitamins and doses used in VISP, NORVIT, and HOPE 2 trials.

	B_{12}	B_6	Folic acid
VISP[10]			
High-dose formulation group	0.40 mg	25.0 mg	2.50 mg
Low-dose formulation group	0.006 mg	0.2 mg	0.02 mg
NORVIT[11]			
A group	0.40 mg	40.0 mg	0.80 mg
B group	0.40 mg		0.80 mg
C group	—	40.0 mg	—
D group	—	—	—
HOPE 2[12]			
Treated group	1.0 mg	50.0 mg	2.50 mg
Placebo control group	—	—	—

level was reduced by 18% there was no effect on the primary endpoints of stroke, CAD, or death. However, the baseline homocysteine level was an independent predictor of vascular events.

The Norwegian Vitamin Trial (NORVIT).[11] This trial examined the potential benefits of vitamin B therapy in patients with acute myocardial infarction. A total of 3749 patients who had myocardial infarction within 7 days of beginning therapy were followed for 5 years on average. The primary endpoints were recurrent myocardial infarction, stroke, or sudden death. Treatment with folic acid and vitamin B_{12} reduced the Hcy level by 27% on average (from 13 to 9.6 μmol/L), but had no effect on the endpoints. On the contrary, in the group treated with folic acid, vitamin B_{12}, and B_6, there was a trend toward an increased risk of vascular events, although this was only observed in patients with homocysteine levels greater than 13 μmol/L at baseline. As in the VISP study, the baseline homocysteine level was a significant predictor of vascular events.

Heart Outcomes Prevention Evaluation (HOPE) 2.[12] A recent Canadian trial examined whether prolonged administration of folic acid with vitamins B_{12} and B_6 reduces the risk of major vascular events in persons at high risk of cardiovascular events. In this study, 5522 patients with vascular disease or diabetes and another risk factor were followed for 5 years on average. While treatment reduced the Hcy level by 18% to 20%, more participants in the vitamin treatment group were hospitalized for unstable angina. As in the VISP and NORVIT studies, there was no effect on the study's vascular endpoints (death from cardiovascular causes, myocardial infarction, or stroke). And once again, the baseline homocysteine level was a statistically significant predictor of cardiovascular events.

Possible reasons for results

While the epidemiological studies clearly associate homocysteine level with cardiovascular outcomes,[5] the results of the three clinical trials described here strongly suggest that treatment with vitamins does not improve outcomes.

We are thus faced with a paradox. While homocysteine levels predict the likelihood of cardiovascular events and, for that matter, cardiovascular[4,7,13] and noncardiovascular death,[13] reducing the level of homocysteine by up to 27% does not appear to influence these events. There are several possible explanations.

Recently, Spence[14] has argued that the major cause of hyperhomocysteinemia, particularly in the elderly, is vitamin B_{12} deficiency, and that the dose of vitamin B_{12} used in all of these trials (see Table 3) was not sufficient. Another less likely possibility is that the relatively small decreases in homocysteine are insufficient to influence outcomes. Perhaps the most plausible explanation is that while homocysteine is a good marker of risk of either cardiovascular or total mortality, it is not the root cause of the problem. Other metabolic pathways that are involved in homocysteine metabolism should be explored for causal relation to the observed pathologies.

In a recent editorial, Loscalzo suggested that vitamin therapy "has other, potentially adverse effects that offset its homocysteine-lowering benefits."[15] He proposed three possible mechanisms: promotion of cell proliferation in the plaque by folic acid through its role in the synthesis of thymidine; increased methylation potential by folic acid and vitamin B_{12} (including DNA methylation), which could result in promoting development of plaques; and inhibition of nitric oxide synthase as a result of methylation of l-arginine to asymmetric dimethylarginine.

Two important lessons

What can we learn from these studies and observations? The first lesson is that *association* is not the same as *causation.* While homocysteine has been proven to act as a predictor of vascular events, lowering homocysteine levels

has not been shown to influence outcomes. We should not plunge into treatment of conditions or metabolites that are associated with specific outcomes until there is a clear causal relationship. In retrospect, the fact that the *MTHRF* polymorphism itself was not associated with vascular events should have been a warning to us not to start vitamin treatment in patients with mild to moderate hyperhomocysteinemia.

A second lesson is that we should not assume absence of harm when prescribing a combination of "harmless" substances in accepted dosages—something already learned with vitamin E.[12,16,17] While we tried to justify using vitamin therapy for lowering Hcy by assuming that vitamins are not toxic and that any treatment based on them is not harmful, there are suggestions from both the NORVIT and HOPE 2 studies that in fact some of the study conditions might have been precipitated or worsened by the vitamin treatment.

Clinical implications

Should we measure homocysteine and treat high levels with vitamins? First, while the homocysteine level is a sensitive indictor of vitamin B_{12} deficiency, it should not replace measurement of vitamin B_{12}. Second, treatment of very high levels, such as those seen in homocysteinuria, should be considered since these levels are the cause of underlying vascular events in this disorder and are known to respond to vitamin treatment.[18] Third, it may still be of value to measure homocysteine levels in those rare patients with severe vasculopathy and no obvious traditional risk factors. Similarly, measurement may be of use in patients with a disastrous family history of vascular disease. In these patient categories, if homocysteine values are very high (i.e., >20–30 μmol/L) treatment may be considered.

Although the hypothesis that high homocysteine levels contribute to atherogenesis cannot be rejected, treating mild to moderate hyperhomocysteinemia with folic acid and B vitamins is clearly not indicated based on the results of recent clinical trials.

Competing interests

None declared.

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