

Thematic Article

Cardiovascular risk in the Asia–Pacific region from a nutrition and metabolic point of view: vitamin deficiencies

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In the past, recommended vitamin or micronutrient intakes have often been based on levels that were adequate to prevent clinical deficiencies from developing. Once these levels were reached, clinicians and nutrition scientists generally attributed little value to higher vitamin intake from supplements or food sources. Evidence has continued to mount showing that the intake and serum concentration of certain vitamins above those necessary to prevent clinical deficiencies, might importantly influence health status. This paper discusses the association of anti-oxidant vitamins and cardiovascular disease, and the association of low intake or serum concentrations of folate, vitamin B6 and vitamin B12, and elevated serum homocysteine, resulting in an increase in vascular disease risk.

Key words: anti-oxidant vitamins, folic acid, homocysteine, vitamin B12, vitamin E.

Introduction

Cardiovascular disease (CVD) is the major cause of morbidity and death in several countries, including those in the Asia–Pacific Region. Smoking cessation and reductions in cholesterol levels and blood pressure have been shown to be effective strategies in the prevention of CVD. However, these classical CVD risk factors cannot fully explain why some people develop myocardial infarction, stroke and other CVD, but others do not. Many emerging risk factors have been investigated. Among these, decreased anti-oxidant vitamins and elevated plasma or serum levels of homocysteine (hyperhomocysteinaemia) are of particular interest.

1. Anti-oxidant vitamins

Eating fresh fruit daily was associated with a 32% reduction in mortality from cerebrovascular disease, a 24% reduction in ischaemic heart disease and a 21% reduction in all-cause mortality.¹ Some of the epidemiological investigations suggest that high vitamin E plasma levels may be associated with a reduced risk of coronary heart disease (CHD). However, the results involving vitamin E supplementation do not consistently show benefit. The results of the Dietary Approaches to Stop Hypertension (DASH) study may encourage increased consumption of fruits and vegetables, perhaps up to the 10 daily servings.² Similarly, vitamin C supplementation may also be beneficial to those with a family history of hypertension or a tendency to mild blood pressure elevation.³

Many believe that if enough of an essential nutrient is good, then more is better. However, naturally occurring anti-oxidant vitamins can cause adverse effects when large amounts are taken for prolonged periods, although they are vital dietary components. In addition, from available evidence we cannot yet answer the question ‘do micronutrient supplements actually improve health or decrease risk of disease where food cannot?’. Another area of concern about supplementation is how much suppression of oxidation may be compatible with good health,

as toxic free radicals are required for defence mechanisms. As yet, there are no clear guidelines from medical reviews on dose–response relationships for anti-oxidants.

Although many anti-oxidant vitamins such as vitamins C and E and β -carotene, have multiple anti-oxidant properties, they can also act as a pro-oxidant in vitro, especially in the presence of metal ions. Mixing vitamin C with iron or copper ions can generate free radicals and cause lipid peroxidation. Whether these pro-oxidant effects are relevant in vivo probably depends on the availability of metal ions. In the healthy human body, metal ions appear largely sequestered in forms unable to catalyse free radical reactions. Therefore, the anti-oxidant properties of vitamin C probably predominate over pro-oxidant effects.⁴ In a study of vitamin E in patients with coronary disease (the Cambridge Heart Anti-oxidant Study, CHAOS), vitamin E treatment (800 IU/day for 2 years or 400 IU/day for 1 year) reduces the risk of non-fatal myocardial infarction by 77%. However, the incidence of cardiovascular death increased by 18% compared to the placebo. Higher doses frequently have been related to a greater risk of CVD or death than lower doses.⁵

Dietary fat may contribute to the causation of atherosclerosis through impairment of endothelial function. Recently, it was shown that pretreatment with anti-oxidant vitamins (1 g vitamin C and 800 IU vitamin E) blocked the transient reduction of endothelial function after a high-fat meal, suggesting potential use of vitamin administration to prevent and manage CHD.⁶

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2. Homocysteine metabolism-related vitamins

Patients with hyperhomocysteinaemia have a twofold to threefold increased risk of developing CVD or venous thrombosis. Reduction of plasma homocysteine levels by vitamins may therefore be of major clinical importance. Several studies have investigated the homocysteine-lowering properties of vitamin B6, vitamin B12, or folic acid alone or in combination.

2.1 Metabolism of homocysteine

Homocysteine is a sulfur-containing amino acid formed during the processing of methionine (Fig. 1). In plasma, approximately 70% of homocysteine circulates in a protein-bound form; approximately 25% combines with itself to form the dimer homocystine; and the remainder (< 5%) combines with other thiols, including cysteine, to form disulfide (a homocysteine–cysteine mix) or circulates as the free thiol compound.⁷ Homocysteine may increase risk of CHD through direct toxicity to endothelial cells, increased coagulation, decreased endothelial reactivity and stimulation of smooth-muscle cell proliferation (Fig. 2). Higher levels of homocysteine have been observed among patients with peripheral and cerebral vascular occlusion and coronary disease.

Evidence linking moderately elevated blood homocysteine levels to increased risk has focused attention on genetic and lifestyle determinants of homocysteine levels. Folic acid, vitamin B12 and vitamin B6 are required for the metabolism and degradation of homocysteine in the body. Epidemiological evidence suggests that populations with higher plasma concentrations of folate and pyridoxal 5-phosphate (PLP, the active form of vitamin B6) have a lower risk of carotid artery stenosis and CHD. In a retrospective study of 130 myocardial infarction cases and 118 controls, folate intake was inversely associated with CHD risk. During 14 years of follow-up of a

large prospective cohort study of women, the Nurses' Health Study, it was found graded associations between higher intakes of folate and vitamin B, and low risk of CHD.⁸

For folate, lower risks were seen for higher intake from either food or supplement sources. In the US, 80 to 90% of the population has a dietary folate intake less than 400 µg/day (the new recommended daily allowance (RDA)); national averages for folate intake and vitamin B6 are estimated at 224 µg/day and 1.51 mg/day, respectively.⁹ In Europe, the mean dietary folate intake is reported to be 291 µg/d for men and 247 µg/d for women. The desired intake was reached by only a small proportion of the European persons studied.¹⁰ Information on folate intake among Asians is limited. Vitamin B6 deficiency is associated primarily with hyperhomocysteinaemia after methionine loading. The risk was lowest with higher intake of food and supplement sources of vitamin B6 combined. Risk of CHD was lowest among women with the highest intake of both folate and vitamin B6. Elevated homocysteine levels after a methionine load and fasting homocysteine levels may be independent predictors of CHD. Recent evidence suggests that vitamin B6 is generally more effective at lowering homocysteine levels after methionine load, and folate more effective at lowering fasting homocysteine levels.

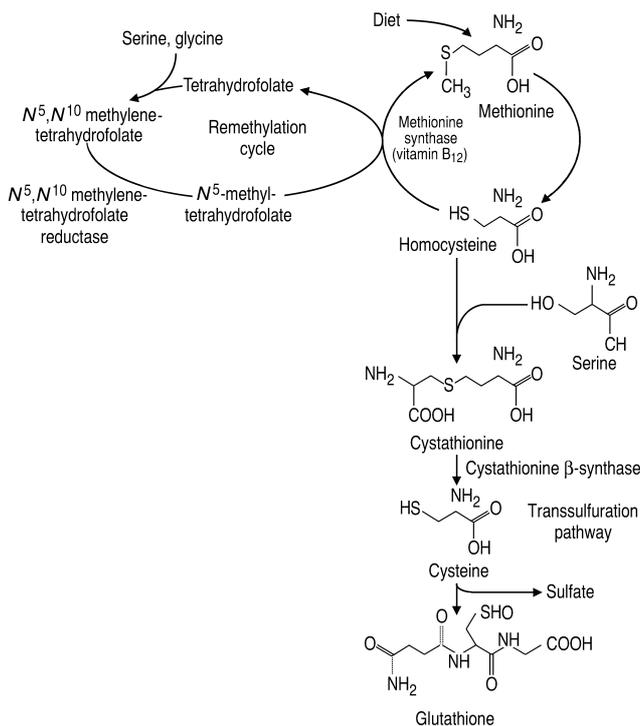


Figure 1. Metabolism of homocysteine.

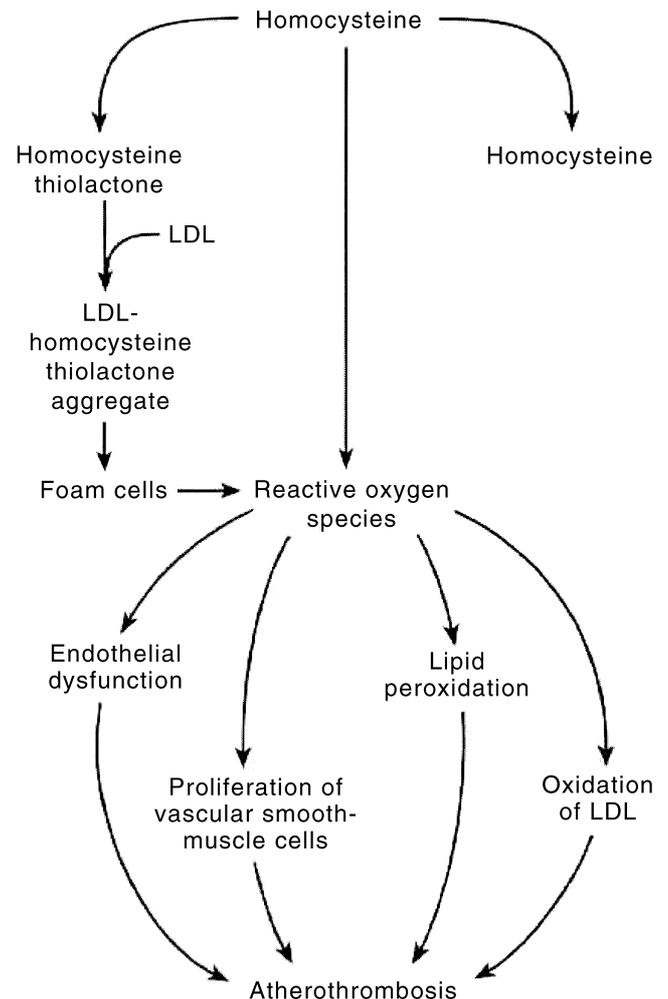


Figure 2. Possible adverse vascular effects of homocysteine. LDL, low-density lipoprotein.

Good food sources of folate include soybeans, liver, leafy green vegetables and berries. Vitamin B6 is found predominantly in bananas, wholemeal breads, cereals, yeast, liver, fish and nuts. Vitamin B12 is found in foods of animal origin; the B12 found in mushrooms is not biologically active.

2.2 Genetic defects in homocysteine metabolism

Severe hyperhomocysteinaemia associated with homocystinuria can be caused by several rare inherited disorders, including homozygous deficiency of cystathionine β -synthase, 5,10-methylenetetrahydrofolate reductase (MTHFR), or methionine synthase or defects in vitamin B12 metabolism.¹¹ The enzyme MTHFR catalyses the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the predominant circulatory form of folate, which serves as a methyl donor for re-methylation of homocysteine to methionine. A common point mutation (677C->T) in MTHFR was recently identified.¹² Heterozygous or homozygous for the common mutation have reduced enzyme activity and increased thermolability.¹³ Homozygosity for this mutation is typically associated with lower plasma folate concentrations and with higher plasma homocysteine concentrations, particularly among those with low plasma folate.^{14–16} This suggests that the mutation itself might affect plasma folate concentration and that the effects on both plasma folate and homocysteine concentrations may be more marked when folate intake is low.¹⁵ It has been hypothesised that the region in MTHFR relating to the common mutation is involved in folate binding and that the enzyme may be stabilised in the presence of folate. It has been suggested that the effect of a mutated MTHFR might be compensated by a higher folate intake.¹⁷

Surprisingly, results of a meta-analysis of 13 studies, in which measurements of plasma homocysteine were made in relation to the three genotypes of MTHFR (TT, CT and CC), and 23 case-control studies of CVD patients and controls, suggest that although the MTHFR mutation is a major cause of mild hyperhomocysteinaemia, the mutation does not increase CVD risk.¹⁸

2.3 Definition and prevalence of hyperhomocysteinaemia

Homocysteinaemia is usually defined by using arbitrary cut-off points, for example, above the 95th percentile or more than two standard deviations above the mean of values obtained from fasting, healthy subjects. Normal plasma homocysteine concentrations usually range from 5 to 15 $\mu\text{mol/L}$.^{19,20} Kang et al. have classified hyperhomocysteinaemia as moderate (homocysteine concentration, 15–30 $\mu\text{mol/L}$), intermediate (30–100 $\mu\text{mol/L}$) and severe (> 100 $\mu\text{mol/L}$) on the basis of concentrations measured during fasting.²¹ However, the definition of elevated homocysteine concentrations is not standardised and substantial differences exist in the 'normal' reference concentrations used in past reviews. Blood homocysteine concentration increases with age and reaches levels of 10–15 $\mu\text{mol/L}$ in healthy adults of middle age (Fig. 1). Elderly persons show homocysteine concentrations of about 10–25 $\mu\text{mol/L}$.²²

The prevalence of hyperhomocysteine depends on the way in which the condition is defined and measured. When the common definition of hyperhomocysteinaemia concentrations of total homocysteine exceeding the 95th percentile

of the distribution in a healthy sample of controls is used, 5% of the normal population will necessarily be defined as having an elevated homocysteine concentration.²³

2.4 Vitamin deficiencies causing hyperhomocysteinaemia

Although folic acid supplementation seems to be the cornerstone in the treatment of hyperhomocysteinaemia, there are some reasons for adding cobalamin and pyridoxine. First, this combination may have a strong effect in subjects with low cobalamin or pyridoxine levels. Second, folate administration alone might mask vitamin B12 deficiency. Addition of cobalamin in a sufficient dose prevents the complications of vitamin B12 deficiency, such as subacute combined degeneration of the spinal cord, even in the case of pernicious anaemia.

Most cross-sectional, retrospective, case-control and prospective cohort studies show positive and dose-dependent associations between blood concentrations or dietary intake of folate, vitamin B6 and vitamin B12, and CVD risk. However, the epidemiological data are not entirely consistent and it cannot fully exclude the possibility that folate and vitamins B6 and B12 may have an association with CVD risk and atherogenesis that is independent of homocysteine concentrations.

2.5 Therapies to decrease plasma homocysteine concentrations

To date, no published randomised clinical trials have evaluated the effects of decreasing homocysteine levels on major cardiovascular events. The ability of randomised clinical trials to detect a therapeutic effect, if one exists, depends on the choice of the population, the specific treatment regimen and the duration of therapy. Targeting persons at high-risk for fatal and non-fatal cardiovascular events; enrolling a sufficiently large sample; maximising folic acid, vitamin B6, and vitamin B12 doses; and allowing for a sufficiently long duration of treatment represent the best strategies in the design of randomised clinical trials evaluating the effects of decreasing homocysteine concentrations. Furthermore, it also remains to be determined whether normalising homocysteine concentrations will improve CVD morbidity and mortality.

Most patients respond to multivitamin treatment within 4–6 weeks of initiating therapy, but may occur in as little as 2 weeks, irrespective of the cause of high homocysteine levels. Folic acid, alone or combined with vitamins B6 and B12, reduces plasma homocysteine levels even in people who are not frankly vitamin deficient.^{17,22} Interestingly, the reduction in mortality from cardiovascular causes since 1960 has been correlated with the increase in vitamin B6 supplementation in the food supply.²³

A recent meta-analysis of the effects of folic acid-based supplements on basal plasma homocysteine concentrations demonstrated that the proportional and absolute reductions in plasma homocysteine concentration produced by folic acid supplements were greater at higher pretreatment plasma homocysteine and at lower pretreatment blood folate concentrations.²⁴ Folic acid, vitamin B6 and vitamin B12 differ in their potential to influence the homocysteine concentration. Folic acid seems to play the key role in lowering homocysteine. Supplementation with either folic acid alone or a combination with vitamin B12 was associated with a reduction in basal plasma homocysteine concentrations. However,

the addition of vitamin B6 did not provide further benefit. This meta-analysis did not evaluate the effects of vitamin therapy on homocysteine concentrations after methionine loading, which may be more dependent on vitamin B6.

The minimum daily dosage of folic acid that has maximal efficacy in decreasing plasma homocysteine concentrations is approximately 0.4 mg.^{24,25} Higher daily dosages are no more effective, except perhaps in patients with renal failure, and lower daily dosages of 0.1 mg seem to be inadequate. However, because the response to therapy to decrease homocysteine concentrations is not uniform and depends on such factors as genotype for enzymes involved in the metabolism of homocysteine and folate, the status of vitamins B6 and B12, and nutritional needs, multivitamin doses for the treatment of hyperhomocysteinemia may need to be modified depending on the response of the individual patient.

A possible side-effect of folic acid therapy is progressive neurologic damage (subacute combined degeneration of the spinal cord) in persons with subclinical vitamin B12 deficiency. In these patients, folic acid therapy may mask the development of the haematologic manifestations of this deficiency. However, this uncommon complication can be avoided by ruling out vitamin B12 deficiency before beginning folic acid therapy or by supplementing folic acid therapy with vitamin B12 therapy. A vitamin B12 dosage of 400–1000 µg/day is suggested because the recommended daily intake of vitamin B12 is approximately 2 µg and only 1 to 3% of oral vitamin B12 is absorbed by simple diffusion.

The major potential side-effect of vitamin B6 therapy is sensory neuropathy, a rare complication largely confined to patients who are treated for months to years with dosages exceeding 400 mg/day. The dosages of vitamin B6 that are used to treat mildly and moderately elevated total plasma homocysteine levels are usually much lower than this (25–50 mg/day).

Since January 1998, the USA Food and Drug Administration has mandated that food products made with cereal or flour be fortified with 140 µg of folic acid per 100 g of flour for the prevention of neural tube defects. A similar policy was implemented in Australia.²⁶ Although a recent study showed that a breakfast cereal providing 127 µg of folic acid per day reduced total plasma homocysteine levels by a mean of only 3.7%,²⁵ it remains to be demonstrated what effect the widespread fortification of foods with folic acid would have on plasma homocysteine levels.

Conclusion

While we cannot conclude that increasing vitamin intake will reduce the risk of vascular disease, a strong case can be made for prevention of the marginal or manifest vitamin deficiency states that may contribute substantially to this important risk factor for CVD. Efforts to prevent deficiencies of folate, vitamin B6 and vitamin B12 in the increasing number of the population over the age of 65 years would have added impetus.

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