

Homocysteinaemia, vascular disease and optimal folate status

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Introduction

Dietary intakes of folate as currently recommended should provide adequate folate status to prevent clinical and subclinical deficiency in healthy people. However, there is now increasing scientific evidence to suggest that the achievement of optimal folate status may be desirable. An optimal folate status (which has a well-established role in the prevention of neural tube defects, or NTDs) may have an important role in the prevention of vascular disease via its effect on homocysteine (an elevated plasma level of which is rapidly emerging as a strong and independent vascular risk factor). Optimal folate status will only be achieved by levels of intake greater than currently provided by a typical diet.

The concept of optimal versus adequate folate status

The term 'optimal nutrition' has evolved in recent years in recognition of the finding that, at least for some nutrients, there may be specific health benefits from optimising levels of intake well above those considered adequate for the prevention of the specific disease associated with nutrient deficiency (i.e. the traditional basis for setting dietary recommendations).

Folate is perhaps one of the best examples of a nutrient for which optimal versus adequate intake can be clearly understood. For example, the protective role of folic acid (the synthetic form of the vitamin) against both recurrence of NTDs is now universally recognised. The mechanism whereby folic acid protects against NTDs appears to be by way of overcoming a partial block in folate metabolism, rather than correcting a nutritional deficiency. Thus, national committees worldwide have set folate/folic acid recommendations for the prevention of NTDs at levels of intake well above that was previously recommended on the basis of being adequate to prevent clinical (megaloblastic anaemia) or subclinical (low red-cell/serum levels) folate deficiency.

More recently, evidence is emerging which suggests that achievement of optimal folate status may have an impact beyond its established protective effect against NTD. In particular, a potential role in the prevention of vascular disease mediated via its effect on plasma homocysteine.

Hyperhomocysteinaemia: a new risk factor for vascular disease

There is now evidence from over 80 clinical and epidemiological studies including more than 10,000 patients which indicates that an elevated level of plasma homocysteine (hyperhomocysteinaemia) is a strong and prevalent risk factor for atherosclerotic vascular disease in the coronary, cerebral and peripheral vessels, and for arterial and venous thromboembolism. The evidence of risk of vascular disease with elevated homocysteine (gathered from case control and prospective studies) suggests that there is a continuous dose-response across the entire range of homocysteine levels, with risk estimated to increase by between 41% and 84% for each 5µmol/L increase in plasma homocysteine; that the risk is similar to and independent of the conventional risk factors, but may enhance the effect of risk factors such as hypertension and smoking; and that elevated homocysteine appears to be a particularly strong risk factor for cardiovascular mortality.⁵

Clinical studies indicate that an elevated homocysteine level is associated with both atherosclerosis and venous thrombogenesis. Possible mechanisms by which elevated homocysteine levels lead to the development and progression of vascular disease have not been fully elucidated, but several have been proposed (to date largely based on in vitro and animal studies). These include promotion and platelet activation and enhanced coagulation, increased smooth muscle cell proliferation, cytotoxicity, induction of endothelial dysfunction and stimulation of LDL oxidation.

Causes of elevated plasma homocysteine

Elevated homocysteine levels arise as a result of both genetic and nutritional factors. Intracellular homocysteine is metabolised either by transsulphuration to cysteine (requiring vitamin B6 as a cofactor) or by remethylation to methionine. Folate (together with vitamin B12) is essential for the latter pathway. Suboptimal folate status is considered to be the most common reason for an elevation of plasma homocysteine levels, while intervention with folic acid is known to lower levels. A study by Selhub et al identified inadequate folate intake as the main determinant of homocysteine-related increase in carotid artery stenosis.

Convincing evidence of the potential role of optimal folate intake in the primary prevention of coronary heart disease (CHD) has recently been provided by a large prospective study of 80,000 women during a 14 year period. The study has shown graded associations between folate intakes and risk of CHD, with highest risk of CHD mortality in women with the lowest intakes of folate.

Amongst the genetic factors implicated in elevated homocysteine, a common point mutation (C677 to T) in the gene for a key enzyme in folate metabolism (methylenetetrahydrofolate reductase, or MTHFR) which results in thermolability with impaired enzyme activity, has recently been identified. Individuals who are homozygous for thermolabile MTHFR (typically 10% of the general population) have elevated homocysteine levels. However, the vascular risk associated with this genetic predisposition appears to be modifiable by achievement of a high folate status. Establishing optimal folate status may therefore be particularly important in the prevention of vascular disease in the face of predisposing genetic factors.

Intervention studies assessing the effects of folic acid on plasma homocysteine

The administration of folic acid at high doses is well documented to lower plasma concentrations of homocysteine. A recent meta-analysis of 12 randomised, controlled trials of folic acid supplementation (totalling 1,114 individuals) has shown that folic acid in the range 0.5-5mg/d lowers homocysteine by about 25%. However, the question of whether low dose folic acid intervention (e.g. in the range 0.1-0.4mg/d) can lower plasma homocysteine levels is the important one from a public health viewpoint. This is because these are levels which would be achievable through dietary modification or folic acid fortification; higher levels could only ever be reached by supplementation and therefore would have very limited potential in the primary prevention of vascular disease.

One recent study examined homocysteine-lowering in response to low-dose folic acid in the range 100-400µg/d in a 26 week intervention study. This study showed that approximately two-thirds of apparently healthy individuals have plasma homocysteine concentrations which may be lowered in response to low dose folic acid, suggesting suboptimal folate status. It also suggested that 200µg/d folic acid was an optimal level (i.e. 100µg/d significantly lowered plasma homocysteine, with 200µg/d producing a further significant decrease; while increasing the dose to 400µg/d for a further 14 weeks produced no further homocysteine-lowering response).

The finding that optimal folate status, with respect to homocysteine-lowering, can be achieved with a dose as low as 200µg/d folic acid (over the above typical dietary levels) has important implications for fortification programmes which should not be based on unnecessarily high doses of folic acid.

Fortification of foods with folic acid: new US legislation

In January 1998, the US Food and Drug Administration implemented new legislation requiring all enriched grain products to be fortified with folic acid at a concentration of 1.4µg/g product, a strategy projected to result in a mean additional intake of 100µg/d folic acid in the population. This new policy was primarily aimed at preventing NTD births, but there may well be benefits in reducing vascular disease.

Elsewhere the question of implementing a mandatory folic acid fortification policy is still under debate. Currently in Ireland and the UK, folic acid fortification of bread and breakfast cereal is permitted on a voluntary basis, thereby the decision to consume goods fortified with the vitamin lies with the consumer.

Conclusion

Accumulating evidence points to a probable role for folate in the prevention of vascular disease. Randomised, controlled trials (many of which are now underway) will eventually confirm whether the treatment of elevated homocysteine levels by folic acid supplementation will affect the incidence and severity of vascular disease. In the meantime, folic acid is known to be very effective at lowering plasma homocysteine and intervention at physiological levels of intake appears to be sufficient for optimal effect.

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