Homocysteine, vitamins and sex

In recent years, researchers have paid considerable attention to the possible role of homocysteine and the B vitamins in heart disease causation. Numerous studies, both prospective and retrospective\(^1\), have shown elevated levels of total plasma homocysteine (tHcy) to be a strong risk factor for cardiovascular disease, although it remains uncertain whether homocysteine itself plays a causative role, or acts as a proxy for global cardiovascular risk. High levels have also been shown to correlate with 5-year mortality risk in established heart disease\(^2\). A number of mechanisms have been proposed whereby homocysteine may have a direct adverse effect on the vasculature, with growing evidence that it impairs endothelial function. Vitamins B\(_6\), B\(_{12}\) and folic acid can reduce tHcy levels, with daily folic acid supplementation producing the largest percentage reduction\(^3\). Several studies are in progress to determine whether a concomitant reduction in heart disease mortality results from vitamin supplementation.

Homocysteine derives from dietary methionine and can be reconverted to methionine in a folate- and vitamin B\(_{12}\)-dependent reaction, or to cysteine in a vitamin B\(_6\)-dependent reaction\(^4\). Two measures of tHcy are commonly used. Mostly, fasting tHcy is measured, but many studies also carry out post-methionine load measurements in which methionine is measured, but many studies also carry out post-

Unlike previous studies, the current paper found only slight evidence of a post-menopausal rise in fasting tHcy over and above the age-related rise. However, a much larger effect was observed on post-methionine tHcy levels. Again contradicting earlier studies, the authors found that the relationship between fasting tHcy was stronger in pre- than in post-menopausal women. The lower level of tHcy in pre-menopausal women is likely to be due to oestrogen, which may have an up-regulatory effect on the hepatic enzyme betaine:homocysteine methyltransferase\(^4\), although Verhoef et al. suggest that the observed hormonal effect is mediated chiefly through effects on muscle mass. It has been proposed that the lower levels of tHcy in pre-menopausal women may partially account for the low incidence of vascular disease in this group, while the rise in tHcy seen post-menopause may account for the rise in disease incidence approaching male levels.

Mean vitamin levels did not differ between the sexes, and thus failed to account for sex differences in tHcy. Whilst low levels of vitamin B\(_6\) constituted a greater risk in women than in men, the reverse was true for folate. The authors suggest that this is due to an increased demand for folate in males, to supply methionine for creatinine formation. The correlation between vitamin B\(_6\) and vascular disease was partially independent of tHcy levels, and is suggested to relate to an effect on clotting mechanisms and cholesterol levels.

The interaction of homocysteine with known risk factors poses certain questions relating to its status as an independent risk factor for cardiovascular disease. It has been suggested that the ‘homocysteine theory of atherosclerosis’ supplies a unifying mechanism for the action of numerous risk factors. Support for this view comes from experiments in vitro and in animal models showing a direct effect of homocysteine on the vasculature\(^1\).

Other researchers have suggested that elevated homocysteine is an epiphenomenon occurring as a result of vascular damage, with no primary role in disease causation. This view is supported by the body of evidence showing that homozygosity for the
thermolabile variant of methylenetetrahydrofolate reductase is not a major risk factor for cardiovascular disease. This well-studied variant causes mild elevation of tHcy in subjects with suboptimal folate levels, and would thus be expected to constitute a considerable risk factor were homocysteine itself toxic to the vasculature[6].

It is clear that further research is needed to unravel the network of cause and effect in the complex relationship between homocysteine and vascular disease. Meanwhile it will be necessary to stratify samples by age, sex and other variables in order to control for the differences in tHcy distribution in various subgroups of the population. Detailed analyses of the variation of tHcy within a study population should facilitate the interpretation of results from future studies.

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References