



## Homocysteine - call off the funeral

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There is strong evidence from prospective studies(1;2) that plasma total homocysteine (tHcy) is a strong, independent, graded risk factor for vascular outcomes. There are many mechanisms by which tHcy can increase vascular risk, including impairment of endothelial function, increased coagulation, increased oxidative stress and oxidation of LDL. Such mechanisms were reviewed in the VISP methodology paper(3).

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Since 1998, when folate fortification of grain products was mandated in North America, the principal nutritional determinant of tHcy is vitamin B12.

We showed that serum B12 was strongly related to both tHcy and to total carotid plaque area (4), a quantity that strongly predicts vascular outcomes (5). We also found that vitamin therapy to reduce tHcy halted progression of carotid plaque, among patients whose plaque area was progressing despite treatment of traditional risk factors(6). In patients undergoing coronary angioplasty, treatment with folate/B6/ and a dose of B12 equal to that used in VISP reduced restenosis (7) and subsequent events (8) but in a subsequent study using only 1/10th the dose of B12 there was no reduction of restenosis (9).

We hypothesized that in VISP(10) there were a number of reasons why vitamin therapy had no effect on events: Folate fortification of the grain supply in North America coincided with the initiation of the study (it was mandated in the US as of January 1998, but began in 1996 in both Canada and the US as grain producers prepared for the mandated fortification). Thus the difference in mean tHcy levels between the high dose and low dose groups was only 2  $\mu\text{mol/L}$  at the beginning of the study, and decreased to only 1.5  $\mu\text{mol/L}$  by the end of the study. Furthermore, several factors may have largely negated the effect of B12 in the high-dose arm: In VISP, be-

cause of ethical concerns, and in the hope of reducing contamination with non-study vitamins, we did not compare vitamin with placebo, but a high-dose vs low-dose vitamin regimen.

The study vitamin in both arms included the FDAs recommended daily intake (RDI) of all vitamins other than folate/B6/B12. Because of concern about subacute combined degeneration and neuropathy, we included the (RDI) for B12 in the low-dose arm. In both the high-dose and low-dose arm of the study, patients with low levels of B12 (<150 pmol/L) received B12 injections to prevent neurological complications. Furthermore, we used in the high-dose arm a dose of B12 that may have been too low for elderly patients with malabsorption of B12. Rajan et al showed that in elderly patients with B12 <221 pmol/L, a dose of 1,000 mcg/day was required for adequate absorption of B12; in VISP we used only 400 mcg/day(11). Some of our patients had very high levels of B12 suggesting supplementation with non-study vitamins, so they would be unlikely to respond to the study vitamin.

It is important to understand that doses of vitamin supplements that are given without regard to mealtimes may need to be higher, because intrinsic factor is released in response to feeding. Doses of B12 that are taken at times other than mealtimes may need to be much higher than we previously thought. Finally, although we excluded patients with severe renal failure because such patients have very high levels of tHcy that are known not to respond well to vitamin supplements (12), we used serum creatinine for the entry criterion. Calculated GFR using the Cockcroft-Gault formula showed that 10% of our patients had significant renal impairment, with GFR <47; these patients would be less responsive to vitamin therapy. In the subgroup defined on the basis of these hypotheses(13), there were 2,155 patients, 37% female, with a mean age of 66 + 10.7 years.

Treatment with high-dose vitamins for two years

(folate 2.5mg, B6 25mg, B12 400mcg daily) was significantly associated with a reduction of the combined endpoint of stroke, death and myocardial infarction, compared with low-dose vitamin therapy (folate 20mcg, B6 200mcg and B12 6mcg). Stratification by entry B12 levels showed that baseline B12 status (probably reflecting ability to absorb B12) was an important determinant of response to the vitamin treatment. We concluded that in the era of folate fortification, B12 plays a key role in vitamin therapy for tHcy. Higher doses of B12, and other treatments to lower tHcy may be needed for some patients.

Our findings show that vitamin therapy for lowering of tHcy should no longer be called folate therapy. It should further be understood that B12 deficiency is much more common than most physicians would expect. In our vascular patients, B12 deficiency (defined as a serum B12 <250pmol/L with an elevation of tHcy or methylmalonic acid) was present in 17%. In older populations, the prevalence of B12 deficiency is approximately 20% (14). There is a serious problem with the definition of the normal range for serum B12. In our hospital the normal range is regarded as 160-600pmol/L; however such ranges, based on the mean + 2SD, include many patients with functional B12 deficiency. Newer approaches based on segmented regression analysis suggest that optimal levels of serum B12 required to maintain low tHcy are around 400-500pmol/L (work in progress).

It is difficult to comment on the NORVIT study because it has not yet been published; however it is my understanding that only 400mcg of B12 was used; if the patients were elderly and had renal impairment, and if patients with B12 deficiency were given injections of B12, it would not be surprising that they may not respond.

Despite the pronouncements by the authors of NORVIT that homocysteine is dead, all of the above suggests that the funeral needs to be called off, at least until VITATOPS and other trials are completed. Reference List

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