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EDITORIAL

Renal Failure, Homocysteine and the Pharmacology of Vitamin B_{12}

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EVEN MILD INCREASES in plasma total homocysteine (tHcy)[1] concentrations over approximately 10 μmol/L increase the risk of atherosclerotic disease and venous thrombosis, especially in the presence of other risk factors.[2-9] The evidence that hyperhomocysteinemia is the *cause* of the increased risk is substantial. The genetic disease, homocystinuria, is characterized by tHcy concentrations greater than 100 μmol/L and is associated with malignant atherosclerosis and venous thrombosis[5]; treatments that reduce the hyperhomocysteinemia reduce the frequency of disease events.[10] Direct biologic evidence, both at the tissue and whole-body level, increasingly strongly supports the hypothesis that Hcy is atherogenic and thrombogenic.[2,5,11-19] A recent randomized clinical trial showed that plasma tHcy lowering by means of simple vitamin therapy reduces post-angioplasty coronary restenosis by 50%.[20]

Nowhere is interest in hyperhomocysteinemia greater than among nephrologists, for renal failure causes hyperhomocysteinemia. Plasma tHcy concentrations of approximately 35 μmol/L are typical of end-stage renal disease (ESRD) and represent a strong, independent predictor of the very high risk of cardiovascular events in this disease.[21-24]

Wilcken et al were the first, in 1979 and 1980, to point out the relationship between hyperhomocysteinemia and renal disease.[25,26] They were also the first to point out that B vitamin therapy can mitigate it.[27] Studying renal transplant patients with persisting moderate renal failure, they showed that the combination of large oral doses of folic acid (5 mg/d), pyridoxine (100 mg/d), and intramuscular vitamin B_{12} substantially reduced the elevated plasma homocysteine-cysteine mixed disulfide concentrations in these patients. They went on to study the individual effect of the vitamins by adding them sequentially in an uncontrolled series involving 11 patients. Folic acid was very effective; pyridoxine was ineffective. A single 1-mg injection of vitamin B_{12} reduced disulfide concentrations by 16%, but, since this was not statistically significant, it was disregarded. Noting the common occurrence of folic acid deficiency in renal patients, and the relative rarity of vitamin B_{12} deficiency, they concluded that folic acid is the treatment of choice for hyperhomocysteinemia in renal disease.[27] The many studies subsequently carried out using different doses or forms of this vitamin indicate that 1, 2.5, 5, and 15 mg/d of folic acid are equally effective at lowering plasma tHcy concentrations of maintenance dialysis patients previously naive to vitamin supplementation.[28-35] The average plasma tHcy reduction is approximately one third, a big improvement, but not nearly enough to normalize plasma tHcy levels for most ESRD patients.

In 1996 Bostom et al[36] reported the results of a short, randomized controlled trial involving 27 dialysis patients randomized either to receive 1 mg folic acid/d or a daily oral regimen consisting of 16 mg folic acid, 100 mg pyridoxine, and 1 mg vitamin B_{12}. The combined regimen reduced plasma tHcy by 30% more than the control regimen of 1 mg folic acid/d. Reviews published thereafter assumed that the key ingredient in this regimen was its ultra-high dose of folic acid,[37-39] and several clinical trials followed using various doses and forms of this vitamin. Their results allow us to conclude that the ultra-high dose of folic acid used in Bostom et al's 1996 trial cannot explain the observed benefit. Could vitamin B_{12}, rather than folic acid, be the critical ingredient in Bostom et al's megavitamin cocktail?

So it seemed to us, when we reported, in *Metabolism,* the results of an observational study comparing plasma tHcy concentrations in two McGill University–affiliated hemodialysis units that differ in their use of folic acid and vitamin B_{12}

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supplementation.[40] The patients in the first unit, where 1 mg cyanocobalamin is administered intravenously each month (as well as 1 mg oral folic acid/d), had plasma tHcy concentrations 22% lower than otherwise similar patients in a nearby unit where 5 mg/d folic acid and a standard multiple vitamin containing folic acid and vitamin B_{12} are routinely provided.[40] Dierkes et al[41] had recently reported, in *Metabolism*, that intravenous vitamin B_{12} dramatically reduces plasma tHcy in ESRD patients with subnormal serum vitamin B_{12} concentrations, but the subjects in our study had normal or high serum B_{12} levels. This suggested that the effect we observed is pharmacologic, not nutritional—that *supraphysiologic* vitamin B_{12} has an important Hcy-lowering effect in most ESRD patients as long as at least 1 mg/d of folic acid is also provided. Apart from Wilcken et al's 1981 study, there was no information as to whether vitamin B_{12} has any specific Hcy-lowering effect in ESRD patients whose vitamin B_{12} status is normal,[39] so we carried out an open clinical trial of the effect of supplemental vitamin B_{12} therapy, administering a total of 3 monthly 1-mg subcutaneous injections of cyanocobalamin to maintenance hemodialysis patients with normal or increased serum vitamin B_{12} concentrations. One month after the third injection, the predialysis plasma tHcy concentration was reduced by 13%, a small but highly statistically significant effect.[42] Shortly thereafter Manns et al,[35] also in an uncontrolled trial, reported that the addition of 1 mg/d oral vitamin B_{12} to the standard vitamin regimen of maintenance hemodialysis patients reduced their plasma tHcy concentration by an average of 17%, a statistically and possibly clinically significant effect.

Could *larger* vitamin B_{12} doses than this produce more impressive Hcy lowering? The question is pertinent, because—contrary to what is often assumed—the massive oral vitamin B_{12} doses used up until now in clinical trials,[35,36,43,44] while nominally "megadoses" are far from megadose in their pharmacologic effect. A maximum of approximately 1.5 μg/d of vitamin B_{12} is absorbed via intrinsic factor, and while a second, intrinsic factor-independent transport system exists, its capacity is limited; only approximately 1% of a large oral vitamin B_{12} dose is absorbed via this system. Consequently, normal persons absorb only a few micrograms of vitamin B_{12} following oral doses of 500 to 1,000 μg.[45] This is sufficient to prevent or treat pernicious anemia,[46] but it might *not* be sufficient to improve Hcy metabolism in a manner comparable to the pharmacologic doses of folic acid that have been so extensively tested for Hcy lowering in ESRD. Thus, 15 mg/d of folic acid (40 times the recommended dietary allowance [RDA][47]) increases average serum folate concentrations about 30-fold,[36] whereas 1 mg/d of oral vitamin B_{12} (400 times the RDA for persons over age 50[47]) increases serum B_{12} concentrations 3-fold at most.[35,36,43] In a randomized controlled trial to be published in *Metabolism,* we found that administering 1 mg/wk parenteral hydroxocobalamin to vitamin B_{12}-replete hemodialysis patients increased their average serum vitamin B_{12} concentration 60-fold and reduced their average plasma tHcy concentration 32% below the lowest level that had previously been attained using high-dose folic acid and pyridoxine.[48] This is an unprecedentedly large, clinically important effect that calls for independent verification in other centres.

Further research is called for in this rapidly developing and clinically important area. The cause of ESRD-related hyperhomocysteinemia is debated,[49] but a defect in the remethylation of homocysteine to methionine has been implicated, at least in ESRD.[50] It is conceivable, therefore, that uremia induces a defect in the activity of methionine synthase, or of its newly characterized activating enzyme, methionine synthase reductase,[51,52] which only pharmacologic tissue concentrations of cobalamin can fully overcome or compensate for.

We need to know more about vitamin therapy, cardiovascular risk, and Hcy in chronic renal failure. Naruszewicz et al[53] recently reported in *Metabolism* that combination vitamin therapy in patients with ESRD not only reduced plasma tHcy, but also circulating concentrations of fibrinogen and lipoprotein(a), both of which are important cardiovascular risk factors in ESRD. Is this a direct vitamin effect, or is it mediated by the reduction in plasma tHcy? We also need to study the relationship between Hcy and outcome in patients with only moderate renal failure, for it, too, is associated with hyperhomocysteinemia.[54] Plasma Hcy reduction was recently named as a promising target for renoprotection strategies.[55]

There is good reason to predict that vitamin B_{12} metabolism and therapy will soon be the focus of new attention in the search to understand and mitigate the hyperhomocysteinemia of renal failure.

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