Holotranscobalamin: Not Ready for Prime Time

Requests for the determination of vitamin B12 (B12) status remain a clinical reality but current laboratory methods for this have limitations (1). In recent years, measurement of holotranscobalamin (holoTC), the fraction of B12 that can enter cells, has been proposed as an improvement, and attempts to demonstrate this improvement have used increased serum methylmalonic acid (MMA) and/or total homocysteine (tHcy) as indicators of deficiency of B12. Both MMA and tHcy may be compromised by renal function and other factors, particularly in an elderly population. The clinical utility and analytical aspects of holoTC have recently been reviewed (2) and current evidence merits continued study of the marker, both for diagnosis of B12 deficiency and assessment of vitamin B12 status.

We investigated indicators of B12 status in an elderly population and used low red cell B12 concentrations (RBC-B12) as a biologically different standard of deficiency. Carmel makes several points regarding the shortcomings of B12 status assays and we agree that these extend to RBC-B12. We do not suggest RBC-B12 has a routine role. However, we observed correlations between RBC-B12 and the B12 markers that were as biologically expected. Our primary analysis was based on ROC plot and stepwise multiple linear regression analyses, which do not depend on selecting cutoffs for the dependent markers. ROC plot analysis demonstrated a significant difference in the area under the curve for holoTC (0.9) compared to MMA (0.78) and serum total B12 (0.8). The same significant hierarchy remained whether we selected RBC-B12 concentrations at the lower or higher 95% CI limits of the reference value used. We also found that with the use of RBC-B12 the positive predictive values of total B12 for deficiency were similar to those reported by Matchar et al. (3), who used clinical diagnosis.

Carmel raised the question of iron status confounding the results. Our hemoglobin data indicated that the prevalence of anemia was high in both the RBC-B12 deficient and nondeficient populations (58% and 42%, respectively), which indeed suggests that many individuals probably had iron deficiency. As Carmel notes, our stepwise multiple regression analysis indicated that 44% of the variation in RBC-B12 concentrations was attributable to holoTC. In this analysis, hemoglobin was not a significant factor, suggesting that other causes of anemia, such as iron status, had much less influence than, for example, holoTC.

Concerning the use or misuse of such assays, Carmel (4) gives an excellent account of the diagnosis, treatment, and management of patients with suspected clinical B12 deficiency. He is very cautious with respect to what to do with what he calls subclinical deficiency (5). He concludes that even in elderly patients, until well-designed clinical trials are completed (a goal that we think is problematic) supplementation has unknown value and specific intervention is not warranted (4). He suggests treating low B12 accompanied by increased MMA or tHcy by injection, which complicates ruling in or out dietary deficiency. This approach would leave follow-up of such patients open.

Many requests for determination of B12 status are for patients without clinical symptoms and are based on the view that the presence of low B12 status could have a detrimental effect in the maintenance of the long-term integrity of brain function, even if evidence of functional deficiency in terms of anemia or neuropathy is not an immediate concern. Most clinicians and, we are sure, most patients given the information would not feel content with accepting a subclinical (or suboptimal) B12 status during their advancing years.

The issue then reverts to why patients develop impaired B12 function in the first place, i.e., whether impairment arises from inadequate intake or malabsorption of B12, or a combination of both. The question of which scenario exists must be established because the respective options for treatment are completely different: either dietary supplements—probably for life—or intramuscular B12 injections, certainly for life. A percentage of patients with anti-parietal cell or anti–intrinsic factor antibodies and/or megaloblastic anemia or neuropathy will obviously need injections. We suggest that a possible way forward clinically would be to administer physiological oral supplements of B12 for a period of 1 month to all patients with low B12 and either raised MMA or tHcy. If there is no improvement, or if deterioration occurs, it would seem clear that, to obtain an adequate B12 status, the patients need intramuscular injections every 3 months for life. The actual cause of the malabsorption or the patients’ inability to be maintained on supplements would then be irrelevant.

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