Reply to LR Solomon

Dear Editor:

We thank Solomon for his observations and comments regarding our recent article on biochemical and neurologic responses to vitamin B-12 treatment in asymptomatic Chilean elderly (1). Our article highlighted the most important effects of treatment; in this response to Solomon’s questions, we provide additional details.

Serum vitamin B-12 <120 pmol/L was used as a cutoff to define participants who required vitamin B-12 treatment and thus were excluded from the longitudinal intervention trial (to be reported elsewhere). Serum vitamin B-12, holotranscobalamin, methylmalonic acid, and plasma total homocysteine (tHcy) were measured later and used to calculate the combined indicator of vitamin B-12 status (cB-12) (2). The cB-12 values further confirmed that global vitamin B-12 status was indeed low at baseline and that 39 of 51 participants had a vitamin B-12 status below adequacy (cB12 ≤−0.5). None of those classified by cB-12 as vitamin B-12–adequate at baseline became vitamin B-12–inadequate after treatment. All participants in the treatment group had an improved vitamin B-12 status based on cB-12, although isolated vitamin B-12 status markers became abnormal (for ≤1 variable per individual) after treatment in some individuals. Interestingly, all such cases involved participants with serum folate >45.3 nmol/L. However, this effect on single biomarkers could be attributed to limitations of the assays.

In accordance with the premise behind the description of the combined variable, we elected to use it to minimize the variability of single markers. This combined indicator initially was derived from the data sets of 3 studies (2). However, the derivation of cB-12 was optimized in 2015 by using a heterogeneous pooled database (n = 5211) containing measurements from studies conducted in 6 countries. Revised cutoffs and guidelines were developed (3) while incorporating adjustments for age and for plasma tHcy when serum folate was <10 nmol/L. Moreover, a surrogate cB-12 was suggested for calculating the combined indicator in the absence of 1 or 2 of the 4 biomarkers (3).

Because our Chilean study was performed on a limited number of participants, we categorized cB-12 and serum folate concentrations as above and below the median at baseline. The group with a baseline cB-12 below the median and serum folate above the median (>33.9 nmol/L; n = 15) failed on average to attain adequate vitamin B-12 status (i.e., a cB-12 ≥−0.5) after treatment (1). Further interpretation comparing groups stratified by commonly used cutoffs for serum folate (>45.3 nmol/L) and the individual vitamin B-12 indicators is limited by the small sample size. However, we re-stratified the data based on commonly used cutoffs as suggested by Solomon and found that both cB-12 and holotranscobalamin presented a very similar pattern of interaction with serum folate. It is possible that with a greater sample size we would also find an interaction with serum B-12 and methylmalonic acid, but this is less likely with tHcy.

For the purpose of this communication, we developed a neurophysiologic score (nerve score) that combined the sensory latencies for the right (X1) and left (X2) sural nerves and the latency of the right median nerve (X3), which all had significant improvement after treatment (P < 0.0001) (1). The score is calculated as $-\log_{10}(X_1 \cdot X_2 \cdot X_3)$, and higher values correspond to better conduction. We re-explored which of the single variables best predicted the neurologic response and found that cB-12, tHcy, and serum vitamin B-12 presented the strongest correlations with the new neurophysiologic score before and after treatment. Methylmalonic acid and holotranscobalamin showed similar patterns; however, the correlations were weaker.

We currently are exploring the influence of the interaction between serum folate and vitamin B-12 status on peripheral nerve function, more details of which will be published in a forthcoming article. Limitations in the sample size affected our power to detect significant differences in these variables, e.g., 4 participants failed to return for the second neurophysiologic assessment. In 5 others, 10 new sensory potentials appeared after treatment where there was previously none. In our previous analyses, the sensory distal latency of the left sural nerve of elderly in the highest serum folate tertile (>49.9 nmol/L) at baseline was less responsive to treatment. However, this pattern was not observed in the sensory latencies of the right sural nerve or right median nerve. Based on the new neurophysiologic score, we find that participants with a persistently abnormal cB-12 present a lower nerve score than those who became normal (P = 0.04) or remained normal after treatment (P = 0.02). Remarkably, the group with a persistently abnormal cB-12 had higher serum folate at baseline (median = 54.4 nmol/L) than those who became normal (P < 0.001) or remained normal (P = 0.02).

Our results were observed after a single intramuscular injection with 10 mg vitamin B-12, which was effective in restoring adequate vitamin B-12 status for 4 mo based on cB-12 and nearly all individual biomarkers. It is possible that more frequent weekly or monthly vitamin B-12 dosing might lead to greater improvement in both metabolic and neurophysiologic variables. Although we could not categorize the participants as having normal or abnormal peripheral nerve function, our results indicate consistent reductions in sensory latencies of peripheral nerves. This feature is a proxy for faster conductivity in myelinated nerves (4). Higher folate status negatively affected both the biochemical indicators of vitamin B-12 status and nerve conduction. Our results came from a relatively small group of asymptomatic elderly who were excluded from a randomized long-term, placebo-controlled trial. Future analyses and results from the larger longer-term trial will provide further insights. We appreciate the opportunity to provide more details on our study in response to Solomon’s letter.

None of the authors had a conflict of interest with the content of this letter.

Alex Brito
Sergey N Fedosov
Joshua W Miller
Ralph Green
Ricardo Uauy
Lindsay H Allen

From the USDA/Agricultural Research Service, Western Human Nutrition Research Center, Davis, CA (AB; LHA, e-mail: lindsay.allen@ars.usda.gov); Department of Molecular Biology and Genetics, Aarhus University, Aarhus, Denmark (SNF); Department of Nutritional Sciences, Rutgers University New Brunswick, NJ (JWM); Department of Pathology and Laboratory Medicine, University of California, Davis, CA (JWM, RG); and the Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile (RU).

REFERENCES


