If High Folic Acid Aggravates Vitamin B\textsubscript{12} Deficiency What Should Be Done About It?

Mary Ann Johnson, PhD

The most common cause of vitamin B\textsubscript{12} deficiency in older people is malabsorption of food-bound vitamin B\textsubscript{12}. Thus, it is suggested that the recommended daily allowance of 2.4 \(\mu\)g/d be met primarily with crystalline vitamin B\textsubscript{12}, which is believed to be well absorbed in individuals who have food-bound malabsorption. There is concern that high intakes of folic acid from fortified food and dietary supplements might mask the macrocytic anemia of vitamin B\textsubscript{12} deficiency, thereby eliminating an important diagnostic sign. One recent study indicates that high serum folate levels during vitamin B\textsubscript{12} deficiency exacerbate (rather than mask) anemia and worsen cognitive symptoms. Another study suggests that once vitamin B\textsubscript{12} deficiency is established in subjects with food-bound malabsorption, 40 \(\mu\)g/d to 80 \(\mu\)g/d of oral crystalline vitamin B\textsubscript{12} for 30 d does not reverse the biochemical signs of deficiency. Together, these studies provide further evidence that public health strategies are needed to improve vitamin B\textsubscript{12} status in order to decrease the risk of deficiency and any potentially adverse interactions with folic acid.

Key words: cognition, fortification, homocystein

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INTRODUCTION

Vitamin B\textsubscript{12} functions in two mammalian enzymes and is essential for cognition, the nervous system, vascular health, and synthesis of red blood cells.\textsuperscript{1-4} During vitamin B\textsubscript{12} deficiency, decreased activity of methionine synthase may cause trapping of folate as methylfolate.

One consequence of this is that the methyl group is not available to methylate homocysteine, which leads to decreased synthesis of methionine, S-adenosylmethionine, and other components of the methylation cycle, as well as high levels of serum homocysteine. Impaired activity of the vitamin B\textsubscript{12}-dependent enzyme methylmalonyl-coenzyme A-mutase leads to a high level of serum methylmalonic acid, which is useful for the diagnosis of vitamin B\textsubscript{12} deficiency.

VITAMIN B\textsubscript{12} INTAKE AND STATUS

The prevalence of vitamin B\textsubscript{12} deficiency in older adults ranges from 5% to more than 20% depending on the population and the criteria used for assessment.\textsuperscript{1-3,5} The primary cause of vitamin B\textsubscript{12} deficiency is atrophic gastritis, which occurs in 10–30% of older adults. Atrophic gastritis leads to decreased gastric acid, digestive enzymes, and the ability to digest the food-bound forms of vitamin B\textsubscript{12} in meat, poultry, fish, and dairy foods. Another cause of vitamin B\textsubscript{12} deficiency is pernicious anemia, which occurs in about 1–2% of older adults and is associated with loss of the intrinsic factor needed for vitamin B\textsubscript{12} absorption. About 1% of oral vitamin B\textsubscript{12} can be absorbed passively without intrinsic factor, so it is suggested that high oral doses of vitamin B\textsubscript{12} can meet the estimated metabolic requirement of 1 \(\mu\)g/d; typically, oral doses of 500–2000 \(\mu\)g/d are recommended to treat deficiency.\textsuperscript{3,6}

The recommended dietary allowance (RDA) for vitamin B\textsubscript{12} is 2.4 \(\mu\)g/d and it is recommended that the majority be consumed as crystalline vitamin B\textsubscript{12}, because the absorption of this form is apparently not affected by atrophic gastritis. The median dietary intakes of vitamin B\textsubscript{12} in women and men aged ≈60 years are 2.7 \(\mu\)g/d and 3.9 \(\mu\)g/d, respectively,\textsuperscript{7} but the intake of crystalline vitamin B\textsubscript{12} from fortified foods and dietary supplements has not been well quantified in the US population. Multivitamins for older adults generally contain 6 \(\mu\)g to 30 \(\mu\)g, while the few foods that are vitamin B\textsubscript{12}-fortified typically contain 2.5 \(\mu\)g to 6 \(\mu\)g.

Folate is a general term for the vitamin present in many chemical forms and that functions in single-carbon
transfer reactions. Folic acid (pterolymonoglutamic acid) is the most oxidized and stable form of folate and it is rarely present naturally in food. Folic acid is the chemical form of folate added to fortified foods and dietary supplements; it is absorbed to a higher degree than the naturally occurring food folates. Naturally occurring food folates are pteropolyglutamates that contain several additional glutamate molecules. Food folates are hydrolyzed to monoglutamate forms in the gut before absorption across the intestinal mucosa occurs. The monoglutamate form is actively transported across the proximal small intestine by a saturable process; pharmacological amounts of the monoglutamate form are absorbed by a nonsaturable process involving passive diffusion. Monoglutamates, primarily in the form of 5-methyl-tetrahydrofolate, are present in the portal circulation, and much of this is taken up by the liver, where folate is metabolized to polyglutamate derivatives and retained or released into the blood or bile. The main circulating forms are 5-methyl-tetrahydrofolate compounds.

Folic acid-fortified foods such as breads, pasta, and some cereals typically provide about 40 µg per serving. Highly fortified breakfast cereals, most multivitamins, and most “B-complex vitamins” contain 400 µg of folic acid per serving or tablet. The RDA for men and women from the age of 14 years to 70+ years is 400 dietary folate equivalents, which is equal to 400 µg of naturally occurring food folates or about 240 µg of folic acid in fortified foods. In addition, to reduce the risk of neural tube defects (NTD) it is recommended that women capable of becoming pregnant consume 400 µg/d of folic acid from fortified foods and/or a supplement as well as food folate from a varied diet. The upper level is expressed as 1000 µg/d of folic acid from fortified foods and/or supplements for adults aged 19 years and older. In the National Health and Nutrition Examination Survey (NHANES) conducted in 1999–2000 (post-mandatory folic acid fortification), the median folate intake from food in adults aged ≥60 years was 275 µg/d in women and 351 µg/d in men; 39.8% took multivitamins and 7.2% took B-complex vitamins. In analyses that corrected for the measurement error related to NHANES methodology, it was estimated that total folate consumption (including natural folate and folate in fortified foods and dietary supplements) in subjects aged ≥65 years exceeds 1000 µg/d in about 2–4% of men and 1–4% of women; uncorrected estimates ranged up to 8%. In 1998, mandatory folic acid fortification of cereal grain products went into effect in the US. The purpose of folic acid fortification is to decrease the incidence of NTD and this is being achieved. Another benefit of folic acid fortification may be decreased incidence of stroke. Randomized, controlled trials suggested that folic acid supplementation (800 µg/d for 3 years) maintained several aspects of cognitive function that tend to decline with age and decreased the progression of age-related hearing loss.

**POTENTIAL RISKS OF HIGH FOLIC ACID INTAKE**

Despite these apparent benefits of improved folate status, there may be risks associated with high intakes of folic acid. Folic acid can be detected in serum. For example, after 14 weeks of consuming 400 µg of folic acid daily, total folate concentration in subjects’ serum was found to be 33.5 nmol/L and folic acid concentration in serum was 0.48 nmol/L (1.4% of total folate). Compared to this long-term study, acute dosing with folic acid followed by blood collection over the next few hours revealed higher amounts of folic acid in the serum. The toxicity of detectable folic acid in serum and of high folic acid intake in general is unclear and controversial. The increase in serum folate in response to folic acid supplementation is much higher in older people than in younger people. A recent randomized clinical trial suggested that folic acid supplementation (1000 µg/d for 6 years) increased the risk of some types of colorectal neoplasia in those with a recent history of colorectal adenomas.

**DOES HIGH SERUM FOLATE EXACERBATE VITAMIN B₁₂ DEFICIENCY?**

There is also continued concern that high intakes of folic acid may appear to prevent and/or cure the macrocytic anemia often associated with vitamin B₁₂ deficiency. This effect, known as masking of vitamin B₁₂ deficiency, is important because the deficiency is often initially detected by measuring the level of macrocytic red blood cells. However, Mills et al. reported no change in the prevalence of anemia among subjects in the US with low serum vitamin B₁₂ after food fortification. Vitamin B₁₂ fortification of the food supply has been recommended, but the suggested target intake is unclear, ranging from 1 µg/d to 15 µg/d. Improved vitamin B₁₂ status through supplementation and/or fortification would help alleviate the risk of folic acid masking vitamin B₁₂ deficiency. Improved vitamin B₁₂ status may also decrease the risk of NTD.

Two studies with implications regarding folic acid fortification and vitamin B₁₂ deficiency in older adults are reviewed below. The results of the first study suggest that during vitamin B₁₂ deficiency, high serum folate levels exacerbate (rather than mask) anemia and also exacerbate cognitive symptoms. The second study was a dose-finding trial conducted to quantify the relationship between oral vitamin B₁₂ intake and serum vitamin B₁₂.
Table 1. High serum folate may worsen the anemia and cognitive impairment associated with vitamin B12 deficiency in older adults (NHANES 1999–2002)

<table>
<thead>
<tr>
<th>Adverse outcome</th>
<th>B12*</th>
<th>Folate†</th>
<th>N</th>
<th>Adverse outcome (N)</th>
<th>Adverse outcome (%)</th>
<th>High homocysteine (%)</th>
<th>OR (95%CI) full model‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia§</td>
<td>Adequate</td>
<td>Normal</td>
<td>913</td>
<td>32</td>
<td>3.5</td>
<td>12</td>
<td>1.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>Adequate</td>
<td>High</td>
<td>198</td>
<td>5</td>
<td>2.5</td>
<td>7.8</td>
<td>0.6 (0.2, 2.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Deficient</td>
<td>Normal</td>
<td>297</td>
<td>20</td>
<td>6.9</td>
<td>31</td>
<td>1.9 (1.01, 3.6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>Deficient</td>
<td>High</td>
<td>49</td>
<td>7</td>
<td>15</td>
<td>23</td>
<td>4.8 (2.3, 10.4)</td>
</tr>
<tr>
<td>Cognitive impairment¶</td>
<td>Adequate</td>
<td>Normal</td>
<td>826</td>
<td>147</td>
<td>18</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Adequate</td>
<td>High</td>
<td>180</td>
<td>20</td>
<td>11</td>
<td>7.8</td>
<td>0.5 (0.2, 0.96)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Deficient</td>
<td>Normal</td>
<td>253</td>
<td>63</td>
<td>25</td>
<td>31</td>
<td>1.6 (0.95, 2.8)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>Deficient</td>
<td>High</td>
<td>42</td>
<td>19</td>
<td>45</td>
<td>25</td>
<td>4.9 (2.6, 9.2)</td>
</tr>
</tbody>
</table>

- Low serum vitamin B12 status defined as serum vitamin B12 <148 pmol/L or serum MMA >210 nmol/L.
- High folate status defined as serum folate >59 nmol/L (80th percentile).
- Adjusted for age, sex, race-ethnicity, educational status, cancer history, diabetes status, hyperhomocysteinemia (>13 µmol/L), and serum concentrations of ferritin, creatinine, and glucose.
- Anemia defined as hemoglobin <120 g/L in women and <130 g/L in men.
- Cognitive impairment defined as <34, lower 20th percentile, on a version of the Wechsler Adult Intelligence Scale III (maximum=133).


In individuals with food-bound vitamin B12 malabsorption, this information can begin to identify the intake of oral crystalline vitamin B12 that might optimize vitamin B12 status, helping to eliminate concerns about the adverse effects of folic acid.

Morris et al. examined the associations among serum folate, vitamin B12 deficiency, anemia, and cognitive impairment in older adults in NHANES 1999–2000 in the “age of folic acid fortification.” Inclusion criteria included normal serum creatinine concentrations and no history of stroke, heavy alcohol use, recent anemia therapy, or disease of the liver, thyroid, or coronary arteries. Of the 3706 older adults in the survey, 1684 were eligible, 1078 were ineligible, and the eligibility status of 944 could not be determined. Sample sizes for analyses of anemia and cognitive impairment were 1458 and 1302, respectively. Anemia was defined as hemoglobin <120 g/L for women and <130 g/L in men. Cognitive status was assessed using a version of the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III. According to the authors’ documentation, this test involves copying symbols that are paired with numbers, is timed for a maximum of 120 seconds, has a maximum score of 133, and some evidence suggests it is superior to the Mini-Mental State Examination for detecting some signs of dementia. The test assesses speed, sustained attention, visual spatial skills, associative learning, and memory, with speed being one of the primary determinants of test performance. Cognitive impairment was defined as having a test score of <34, which was the 20th percentile of the distribution.

Serum folate and vitamin B12 were assessed using radioassay (Quantaphase II Radioassay Kit, Bio-Rad Laboratories, Anaheim, Calif., United States). Vitamin B12 deficiency was defined as either 1) serum vitamin B12 of <148 pmol/L or 2) serum methylmalonic acid >210 nmol/L, which is the reference range for vitamin B12-replete individuals with normal serum creatinine (note that the MMA methodology differs among NHANES surveys, so the results of various studies may not be comparable). High serum folate was defined as >59 nmol/L, which reflects the 80th percentile distribution in older adults; in some analyses to detect interactions, serum folate was also used as a continuous variable.

Univariate analyses identified several differences between those with adequate and deficient vitamin B12 status. Those with vitamin B12 deficiency were significantly older (72 y vs 70 y) and had lower serum folate (34 vs 39 nmol/L). They were less likely to be male (34% vs 38%), be non-Hispanic black (4.4% vs 8%), have a high school diploma (68% vs 75%), and use supplements (54% vs 71%). They were more likely to smoke (17% vs 12%) and have macrocytosis (6.5% vs 2.7%), anemia (8.3% vs 3.2%), and cognitive impairment (32% vs 15%).

A series of multivariate analyses controlling for several demographic and health-related indices were conducted to identify the relationships of folate and vitamin B12 status with anemia, cognitive impairment, and homocysteine. The prevalence of anemia in participants with normal vitamin B12 status was about 3% and was not affected by folate status (Table 1). However, a significant interaction between folate and vitamin B12 status occurred, such that the deficient vitamin B12/high-
folate group was about twice as likely to be anemic compared to the deficient vitamin B_{12}/normal-folate group (15% vs 6.9%). A statistically significant interaction also occurred for cognitive impairment; in vitamin B_{12}-adequate participants, higher folate status was associated with better cognitive status, but in vitamin B_{12}-deficient participants, the prevalence of cognitive impairment was nearly double in those with high versus normal folate status (45% vs 25%). High homocysteine did not closely track the prevalence of anemia or cognitive impairment; for example, the highest percentage of high homocysteine did not occur in the group with the highest prevalence of anemia or cognitive impairment.

Comments

It was unexpected that high serum folate coexisting with vitamin B_{12} deficiency would worsen both anemia and cognitive impairment. Thus, even though the regression analyses controlled for several potentially important predictors of anemia and cognition, there are some concerns about whether or not a few individuals in the small vitamin B_{12}-deficient/high-folate group may have had some unusual characteristics that skewed the results and contributed to the interaction. Specific questions include the following.

1) Could the overall findings be related to the relatively small sample size of the vitamin B_{12}-deficient/high folate group (N=42–49) compared to the other participants (N=1259–1408)? a) In the vitamin B_{12}-deficient/high-folate group versus the other participants, the number of cases of anemia was 7 versus 57 and the number of cases of cognitive impairment was 19 versus 230. b) Even though demographic characteristics were included in the multivariate regression models, perhaps there were some demographic differences in this small group that may have magnified their response to high folate. For example, compared to blacks, whites have better folate status, but poorer vitamin B_{12} status.^3,31,32

2) Did the causes of high serum folate differ in the vitamin B_{12}-deficient/high-folate group compared to the vitamin B_{12}-adequate/high-folate group? a) Was the vitamin B_{12}-deficient/high-folate group consuming large amounts of folic acid from supplement formulations that might have contributed to the anemia or cognitive impairment, e.g., folic acid supplements with minimal vitamin B_{12} and/or iron? Some dietary supplements marketed to older adults contain minimal or no iron. Also, the amount of vitamin B_{12} in “B complex” supplements ranges from about 6 μg to 100 μg, while the amount of folate is usually 400 μg/tablet. b) Was the vitamin B_{12}-deficient/high-folate group consuming large amounts of folic acid from fortified foods formulated in such a way as to worsen the anemia or cognitive impairment, e.g., breakfast cereals with high amounts of folic acid (e.g., 400 μg per serving) with minimal vitamin B_{12} and/or poorly available iron? c) Did the vitamin B_{12}-deficient/high-folate group have a high prevalence or severity of an undetected infection that might have increased their serum folate? For example, infection with tick-borne fever caused by rickettsia Anaplasma phagocytophilum in sheep led to unusually high serum folate concentrations (in the 300 to 400 nmol/L range).^33 Also, increased serum folate and decreased serum vitamin B_{12} have each been associated with small intestinal bacterial overgrowth in animals, because many enteric bacteria synthesize folic acid that is available for absorption, but bind vitamin B_{12}, which is then unavailable for uptake in the ileum.^34 Similar processes can occur in vitamin B_{12}-deficient humans.\(^2\)

3) What were the primary causes of vitamin B_{12} deficiency in the vitamin B_{12}-deficient/high-folate group and did they differ from the vitamin B_{12}-adequate/high-folate group? Perhaps the vitamin B_{12}-deficient/high-folate group was simply the most vitamin B_{12}-deficient. Possibly, the vitamin B_{12}-deficient/high-folate, compared to the vitamin B_{12}-deficient/normal-folate group were: a) more likely to lack intrinsic factor, suggesting a more long-standing and severe form of vitamin B_{12} deficiency that would, in turn, explain the higher prevalence of anemia and cognitive impairment; or b) more likely to have a lower serum vitamin B_{12} level, intake of total vitamin B_{12}, and/or intake of synthetic vitamin B_{12}, which might also indicate a more long-standing and severe form of vitamin B_{12} deficiency.

4) What was the nature and severity of the anemia in the vitamin B_{12}-deficient/high-folate group compared to the vitamin B_{12}-deficient/normal-folate group? a) Could there be a higher prevalence of iron deficiency-related anemia that might contribute to both the higher prevalence of anemia and cognitive impairment? Vitamin B_{12} deficiency has been associated with low serum ferritin in older adults^5 and was seen in the present study as well (although it was controlled in the regression analyses). b) Could there be a higher prevalence of anemia of chronic disease that might contribute to both the higher prevalence of anemia and possibly cognitive impairment? c) Was there a higher prevalence of gastrointestinal bleeding that could have contributed to the anemia?

In summary, while the vitamin B_{12}-deficient/high-folate group clearly had the highest prevalence of anemia and cognitive impairment among the four vitamin B_{12}/folate groups in this study, the individual cases of vitamin B_{12} deficiency could be explored further. Also, the findings need replication in other studies that include detailed analyses of the dietary and supplement use patterns, as well as the causes and severity of vitamin B_{12} deficiency, anemia, and cognitive impairment.
WHAT IS THE OPTIMAL INTAKE OF CRYSTALLINE VITAMIN B₁₂ IN ELDERLY PEOPLE WITH MALABSORPTION OF FOOD-BOUND VITAMIN B₁₂?

It is recommended that 2.4 μg/d of crystalline vitamin B₁₂ will meet the requirements for those with malabsorption of food-bound vitamin B₁₂ in animal foods. However, Campbell et al. found in the Sacramento Area Latino Study on Aging that 14% of those consuming 2.4 μg of crystalline vitamin B₁₂ from supplements and fortified foods had plasma vitamin B₁₂ concentrations <148 pmol/L (i.e., in the deficient range). Also, in several other cross-sectional surveys of older adults, the risk of poor vitamin B₁₂ status, as assessed by serum or plasma vitamin B₁₂ and/or methylmalonic acid, was not less than 5% until the consumption of vitamin B₁₂ was 9 μg/d.²³ 12–50 μg/d,²⁶ or 25–37.5 μg/d.³⁷ Because 2.4 μg/d appears to offer adequate protection against vitamin B₁₂ deficiency in these cross-sectional studies, there is interest in conducting clinical trials to quantify the requirements for crystalline vitamin B₁₂ in those with malabsorption of food-bound vitamin B₁₂.

In one such study, Blacher et al. randomly assigned people with food-bound vitamin B₁₂ malabsorption from a “frail geriatric population” to one of six oral daily doses of vitamin B₁₂ (2.5, 5, 10, 20, 40, and 80 μg/d) for 30 d to identify the dose that increased serum vitamin B₁₂ by 37 pmol/L (50 ng/ml). Every person entering the Emile Roux Hospital in a suburb of Paris between June 2003 and March 2004 was screened for vitamin B₁₂ status. Those with low serum vitamin B₁₂ (<162 pmol/L) were identified and the following inclusion criteria were applied: 1) 70 y of age; 2) absence of fatal disease, life expectancy >1 month; 3) planned hospitalization duration of >1 month; 4) lack of clinical signs of vitamin B₁₂ deficiency (i.e., Mini Mental Status Examination 23 of 30 points, absence of clinical peripheral neuropathy, absence of clinical signs of subacute combined degeneration of the spinal cord, hemoglobin >100 g/L). Participants also had to show evidence of food-bound vitamin B₁₂ malabsorption, such as 1) low serum vitamin B₁₂ concentration; 2) normal Schilling’s test; and 3) no dietary vitamin B₁₂ deficiencies and at least one of the following conditions: a) gastric disease, including atrophic gastritis, type A atrophic gastritis, gastric disease associated with *Helicobacter pylori* infection, partial gastrectomy, bypass gastric surgery, vagotomy, or Zollinger-Ellison syndrome; b) pancreatic insufficiency resulting from alcohol abuse or cystic fibrosis; c) gastric or intestinal bacterial overgrowth, including achlorhydria, sprue tropical, Ogilvie syndrome; d) chronic drug treatment such as ingestion of acid-sup.

### Table 2. Baseline characteristics of 67 elderly subjects with vitamin B₁₂ malabsorption from food

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>83.3±7.4</td>
</tr>
<tr>
<td>Gender, % female</td>
<td>57</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>121±14</td>
</tr>
<tr>
<td>Mean corpuscular volume, fL</td>
<td>92.7±6.3</td>
</tr>
<tr>
<td>Serum vitamin B₁₂, pmol/L^*</td>
<td>120±49</td>
</tr>
<tr>
<td>Plasma folate, nmol/L</td>
<td>28.7±65.5</td>
</tr>
<tr>
<td>Folate deficiency, %</td>
<td>76</td>
</tr>
<tr>
<td>Plasma homocysteine, μmol/L^†</td>
<td>18.1±6.9</td>
</tr>
<tr>
<td>Plasma methylmalonic acid, mmol/L^§</td>
<td>1870±960</td>
</tr>
<tr>
<td>Total vitamin B₁₂ intake, μg/d</td>
<td>3.1±0.9</td>
</tr>
<tr>
<td>Total folate intake, μg/d</td>
<td>236±93</td>
</tr>
</tbody>
</table>

^*Normal >162 pmol/L.

^†Folate deficiency defined as plasma folate <6.8 nmol/L.

^§Normal <14.6 μmol/L.

with food-bound malabsorption are needed to clarify the
dose-response relationships of oral doses of vitamin B\textsubscript{12} of \(\leq 20\) \(\mu\)g/d, especially if recommendations for fortification and/or supplementation are set below 20 \(\mu\)g/d for this subgroup of the older adult population.

**Comments**

The main strength of the Blacher et al.\textsuperscript{30} study is that it documents the pervasiveness of vitamin B\textsubscript{12} deficiency in hospitalized older adults, as well as the very high prevalence of folate deficiency when the food supply is not fortified with folic acid. Some difficulties in using data from these types of dose-finding trials to develop food-fortification and supplement-use recommendations is that the severe degree of deficiency means that the doses are probably replenishing both the metabolically active body pool as well as body stores. Also, there is no consensus on what constitutes an adequate or optimal serum concentration of vitamin B\textsubscript{12}. The authors’ goal of reaching 148 pmol/L seems rather low, given that some signs of vitamin B\textsubscript{12} deficiency can occur when serum vitamin B\textsubscript{12} concentrations are up to 258 pmol/L.\textsuperscript{5,31,38} The response of serum vitamin B\textsubscript{12} to oral vitamin B\textsubscript{12} was the same at the 40 \(\mu\)g/d and 80 \(\mu\)g/d doses after 30 d, and final concentrations averaged only about 200 pmol/L (Figure 1A).

In addition, these doses of vitamin B\textsubscript{12} did not lower the markedly elevated serum methylmalonic acid, probably for one or more of the following reasons: 1) the doses were too low; 2) renal insufficiency led to decreased renal clearance of methylmalonic acid; and/or 3) intestinal bacteria was the source of methylmalonic acid. If the participants had bacterial overgrowth of the intestine, then some circulating methylmalonic acid may have been derived from this microbial source and may have been unresponsive to increased intake of vitamin B\textsubscript{12}.\textsuperscript{39} The lack of change in serum homocysteine is not surprising given the high prevalence of folate deficiency in this population unexposed to folic acid fortification (76%) and the possibility of renal insufficiency. Eussen et al.\textsuperscript{40} reported that community-dwelling older adults with initial serum vitamin B\textsubscript{12} concentrations of about 208 pmol/L (range 100–300 pmol/L) needed a dose of 100 \(\mu\)g/d for 8 weeks to improve serum vitamin B\textsubscript{12} to about 300 pmol/L, but a dose of more than 500 \(\mu\)g/d for 8–16 weeks was needed to maximally lower serum methylmalonic acid.

**PUBLIC HEALTH IMPLICATIONS**

Together, the studies of Morris et al.\textsuperscript{29} and Blacher et al.\textsuperscript{30} provide further evidence of the need to implement public health strategies to improve vitamin B\textsubscript{12} status in older adults. Cross-sectional studies suggest that supplements containing vitamin B\textsubscript{12} decrease the prevalence of vitamin B\textsubscript{12} deficiency.\textsuperscript{31,35,37} Vitamin B\textsubscript{12} fortification of the food supply has also been recommended, but there is no clear consensus on the appropriate target intake or fortification level. Estimates in the low range include 1 \(\mu\)g/d to provide a portion of the RDA of 2.4 \(\mu\)g/d.\textsuperscript{27} Higher estimates in the range of 12 \(\mu\)g/d to 15 \(\mu\)g/d are recommended to increase body stores of vitamin B\textsubscript{12} to be available when intrinsic factor is lost and the capacity to absorb vitamin B\textsubscript{12} is diminished.\textsuperscript{23} The findings of Blacher et al.\textsuperscript{30} show that once an older adult with food-bound vitamin B\textsubscript{12} malabsorption becomes extremely deficient, intakes of vitamin B\textsubscript{12} of \(\leq 20\) \(\mu\)g/d are unlikely to normalize serum vitamin B\textsubscript{12} or methylmalonic acid in the short term.

The goals of a vitamin B\textsubscript{12}-fortification or supplement-use program will need clarification regarding the
target levels of serum vitamin B₁₂, serum methylmalonic acid, and liver stores of vitamin B₁₂ to provide the metabolic needs for vitamin B₁₂ when absorption begins to fail due to food-bound malabsorption and/or pernicious anemia. Improved vitamin B₁₂ status would help alleviate any effect of folic acid in aggravating vitamin B₁₂ deficiency. Also, improved vitamin B₁₂ status, by lowering the risk of NTD, may promote health in other age groups.²⁸

ACKNOWLEDGMENTS

The editorial assistance of Dr. Dorothy B. Hausman is greatly appreciated.

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