Vitamin B-12 deficiency in the elderly: current dilemmas

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ABSTRACT Vitamin B-12 deficiency is present in up to 15% of the elderly population as documented by elevated methylmalonic acid with or without elevated total homocysteine concentrations in combination with low or normal-normal vitamin B-12 concentrations. Clinical signs and symptoms of vitamin B-12 deficiency are insensitive in elderly subjects and comorbidity in these subjects makes responses to therapy difficult to interpret. Many elderly subjects with hyperhomocysteinemia have undiagnosed vitamin B-12 deficiency with elevated serum methylmalonic acid concentrations. Therefore, such elderly subjects should not receive folic acid supplementation before their vitamin B-12 status is diagnosed. Oral vitamin B-12 supplementation may be effective in lowering serum methylmalonic acid values in the elderly. However, the dose of vitamin B-12 in most common multivitamin preparations is too low for this purpose. Research efforts should be directed toward determining practical methods for diagnosing and treating vitamin B-12 deficiency in the millions of elderly subjects with undiagnosed deficiency. 


KEY WORDS Methylmalonic acid, cobalamin, homocysteine, folate, dementia, elderly, vitamin B-12

INTRODUCTION

Several recent developments make it necessary to reexamine strategies for diagnosing and treating vitamin B-12 (cobalamin) deficiency in the large numbers of elderly subjects with undiagnosed deficiency. The first development was the realization that serum vitamin B-12 concentrations have limited sensitivity and specificity in the elderly. In many cases, both the low and low-normal serum vitamin B-12 concentrations found frequently in elderly subjects are accompanied by elevations in the vitamin B-12-dependent metabolites methylmalonic acid (MMA), total homocysteine (tHcy), or both (1–7). In fact, 50% of those with elevated concentrations of metabolites have a serum vitamin B-12 concentration above the conventional cutoff of 2 SD below the mean in a normal population (1, 2). Elevated MMA and tHcy concentrations respond to therapy with vitamin B-12, given either alone or in combination with other vitamins (1, 4, 5, 8).

A second development is the growing body of evidence that elevations of homocysteine, regardless of cause, are associated with vascular disease; thus, homocysteine-lowering regimens are currently being developed (9–16). A third important development is the federally mandated food folate-fortification program; by January 1998, potentially millions of vitamin B-12-deficient elderly subjects will be exposed to increased dietary folate (17). Thus, there are new questions regarding the diagnosis and treatment of vitamin B-12 deficiency in elderly subjects. We address the relative specificity and sensitivity of the metabolites and vitamin concentrations, the causal role of vitamin B-12 deficiency in hyperhomocysteinemia, the clinical manifestations of vitamin B-12 deficiency, and treatment options in the elderly.

ELEVATED SERUM MMA AND HOMOCYSTEINE IN CLINICAL VITAMIN B-12 OR FOLATE DEFICIENCY

Vitamin B-12 is a known cofactor for two reactions in higher animals (Figure 1 and Figure 2). In the first reaction, l-methylmalonyl-CoA is converted to succinyl-CoA by an adenosylcobalamin-dependent enzyme, l-methylmalonyl-CoA mutase (18). When methylmalonyl-CoA concentrations increase, a specific hydrolase cleaves the D-isomer to MMA (19). The second reaction is the methylation of homocysteine by methionine synthase utilizing a methyl group from N5-methyltetrahydrofolate and methylcobalamin as a cofactor (20). Alternatively, homocysteine is condensed with serine to form cystathionine, in a reaction dependent on pyridoxal 5'-phosphate (21). Cystathionine can be further cleaved to α-ketobutyrate and cysteine (21). MMA concentrations increase to extremely high levels in clinical vitamin B-12 deficiency (22–28) and with inborn errors of cobalamin or mutase metabolism (18). Both clinical vitamin B-12 and clinical folate deficiencies result in elevated concentrations of tHcy, termed hyperhomocysteinemia (28–32). tHcy is also occasionally elevated in subjects with vitamin B-6 deficiency (33, 34). Both tHcy and MMA concentrations increase in renal insufficiency (24, 31, 35–38). tHcy concentrations are usually correlated with serum creatinine, age, male sex, and total cysteine concentrations (39, 40).

During the past decade it became possible to determine the sensitivity and specificity of serum vitamin B-12 and folate concentrations as well as to identify the clinical syndromes associated with various vitamin deficiencies when sensitive and specific assays for serum and urine MMA and tHcy be-
came available. It was shown that MMA concentrations are elevated in nearly every patient with hematologic or neurologic abnormalities due to cobalamin deficiency and that MMA concentrations respond to vitamin therapy (24–28, 41). It was also shown that in inadequately treated patients with known pernicious anemia (those not receiving an adequate number of vitamin B-12 injections), MMA concentrations were most commonly the first indicator to become abnormal (42). At least 5% of subjects with classic, clinically defined vitamin B-12 deficiency have serum vitamin B-12 values above conventional cutoffs (42). Serum tHcy was also found to be elevated in > 90% of subjects with clinical vitamin B-12 deficiency or with megaloblastic anemia resulting from folate deficiency (28). tHcy is slightly less sensitive than MMA concentrations and there are a few vitamin B-12-deficient patients with tHcy elevations only (28). Response to therapy is specific and can be used diagnostically because folic acid treatment does not correct elevated MMA or tHcy in vitamin B-12 deficient patients and vice versa (43). Folate-deficient subjects do not have elevated MMA concentrations unless they have renal failure or volume depletion (28). A significant number of vitamin B-12-deficient patients who have marked elevations of MMA and tHcy have neurologic abnormalities that respond to vitamin B-12, despite the absence of megaloblastic anemia (44). There is an inverse relation between the severity of the neurologic disease and that of the hematologic disease (45). Comparisons of metabolite concentrations with vitamin B-12 concentrations and clinical syndromes showed that serum vitamin B-12 is often nonspecific with a low predictive value (41, 46, 47). Normal concentrations of MMA and tHcy in subjects with low vitamin B-12 concentrations rules out significant clinical deficiency (41).

Several other metabolites, although less sensitive than MMA and tHcy, are also elevated in severe clinical vitamin B-12 and folate deficiencies. Cystathionine and 2-methylcitrinate are frequently elevated in vitamin B-12–deficient patients (48, 49). Serum cystathionine and N-methylglycine (sarcosine) are frequently elevated in folate-deficient subjects (48, 50). Serum cystathionine concentrations were found to be increased in subjects with drug-induced vitamin B-6 deficiency (34), especially after a methionine load. Both cystathionine and 2-methylcitrice acid are more sensitive to poor renal function than are MMA and tHcy (48, 49), and can thus suggest this diagnosis in subjects with borderline serum creatinine values.

**HIGH PREVALENCE OF ELEVATED MMA AND tHcy IN THE ELDERLY**

Because the diagnostic utility of serum MMA and tHcy values was first shown in subjects with severe vitamin B-12 deficiency due to classically defined pernicious anemia (ie, positive for antibodies to intrinsic factor or a positive stage I Schilling test), it became possible to study elderly populations to determine whether their high prevalence of low vitamin B-12 concentrations had metabolic or clinical significance. The combination of elevated MMA with low or low-normal serum vitamin B-12 concentrations, with or without elevated tHcy, was found in 5–15% of elderly populations (1–4, 7, 51). Only a few of these subjects had proven pernicious anemia (1, 2, 5, 52); the rest may have various degrees of food vitamin B-12 malabsorption due to atrophic gastritis (5, 52) or intestinal pathology. Few of these subjects were found to have classic megaloblastic anemia, and comorbidity made interpretation of
neurologic abnormalities difficult (1, 2, 7, 52). Perhaps most surprising was that there were almost as many subjects with elevated MMA or tHcy among those with serum vitamin B-12 concentrations in the low-normal range as there were among those with concentrations in the low range (ie, < 150 pmol/L, or < 200 pg/mL) (1–4, 7). In an evaluation of 548 subjects from the Framingham Heart Study cohort, a cutoff of 260 pmol/L (350 pg/mL) for serum vitamin B-12 was much better able to separate subjects with elevations of MMA from those with normal MMA concentrations (2).
ARE ELEVATED CONCENTRATIONS OF MMA AND tHcy DETRIMENTAL IN THE ELDERLY?

Elevations of serum MMA in elderly subjects in screening studies range from concentrations just above a 2-SD cutoff (> 271 nmol/L) (1, 2) to the high concentrations frequently seen in subjects with severe clinical vitamin B-12 deficiency (28). It is possible that a normal range for MMA determined in younger populations is not valid for elderly subjects. This is unlikely, however, because the elevated concentrations seen in the elderly decrease readily into the normal range when the subjects receive parenteral vitamin B-12 therapy (1, 4, 8, 52, 53). Only in an occasional subject with renal failure do MMA concentrations fail to fall into the normal range with vitamin B-12 therapy. In one study by Rasmussen et al (54), MMA concentrations did not decrease when 252 normal subjects were treated with high-dose oral vitamin B-12 for 2 wk unless the subjects had a baseline concentration > 240 nmol/L. Thus, it appears that elevations of MMA that decrease with vitamin B-12 therapy actually document enzymatic deficiency, because the values cannot be manipulated in normal subjects. In the same study, high-dose oral folate (10 mg/d) caused a marked decrease in serum tHcy even in subjects with tHcy concentrations below the mean (54). The fact that tHcy can be driven to very low concentrations by large amounts of oral folic acid suggests that this decrease cannot always be used as evidence for tissue deficiency, in contrast with the serum MMA concentration response to vitamin B-12 treatment.

It is possible that the elevations of MMA and tHcy found in screening studies in the elderly are of no clinical importance because associated vitamin B-12-deficient megaloblastic anemia is rare in such surveys. Elevations of tHcy, regardless of cause, may be associated with increased vascular disease (10, 11), although there have been no intervention studies to prove any benefit in lowering such concentrations. There has been a historical bias to consider vitamin B-12 deficiency as synonymous with megaloblastic anemia, extending even to the designation of the severe malabsorption disorder due to lack of intrinsic factor as "pernicious anemia". Until recently the specific diagnosis of deficiency depended mainly on the vitamin B-12 concentration, and the purely or mostly neurologic presentations of vitamin B-12 deficiency were considered rare. However, with the confirmatory evidence of elevated MMA or tHcy in addition to serum vitamin B-12, unequivocal vitamin B-12 deficiency can be shown in subjects with mild or completely absent hematologic abnormalities (44).

We do not know what percentage of vitamin B-12-deficient patients have anemia because there are no data from large general population studies that could be used to correlate MMA values with hematologic variables. It is possible that only a minority of the patients with severe biochemical vitamin B-12 deficiency ever develop megaloblastic anemia. Evidence supporting this view can be found in an interesting series of studies published in the Netherlands on infants and young children who had been weaned to a macrobiotic diet that did not contain significant amounts of vitamin B-12 (55–57). These subjects had severe vitamin B-12 deficiency on the basis of high concentrations of serum MMA and tHcy (57), but had only subtle hematologic abnormalities (55). Despite rapid growth status and coexistent iron deficiency, the subjects did not have the severe anemia that might have been expected. They did, however, have developmental and growth abnormalities. The investigators did not provide information on the folate intake of these subjects, but it is possible there was a masking of anemia by high dietary folate, which could be present in a totally vegetarian diet (56).

Severe enzymatic vitamin B-12 deficiency can exist in subjects without frank megaloblastic anemia (44). Data from five patients studied recently at the University of Colorado Health Sciences Center are shown in Table 1. Patients 1 and 2 were selected because they had among the highest MMA values measured in samples sent from the clinics of the University of Colorado Health Sciences Center. In these subjects, MMA concentrations were extremely high despite normal or almost normal complete blood counts. Patient 2 had donated two units of blood for later autologous postoperative transfusion in the weeks before the blood count shown in the table. Patient 4 is interesting because she had a normal vitamin B-12 concentration but an MMA value as high as that of patient 3, whose vitamin B-12 concentration was clearly low. Without anemia and with a normal vitamin B-12 value, many clinicians would assume that patient 4 had normal vitamin B-12 status. However, MMA and tHcy concentrations were elevated in this patient but were not representative of values seen in patients...

### TABLE 1

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>MMA (nmol/L)</th>
<th>Hcy (μmol/L)</th>
<th>MCV (FL)</th>
<th>Hct</th>
<th>Serum B-12 (pmol/L)</th>
<th>Serum folate (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>74300</td>
<td>43.8</td>
<td>98</td>
<td>0.41</td>
<td>33</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>64</td>
<td>M</td>
<td>68600</td>
<td>76.1</td>
<td>110</td>
<td>0.38</td>
<td>&lt;12</td>
<td>ND</td>
</tr>
<tr>
<td>3</td>
<td>83</td>
<td>F</td>
<td>12600</td>
<td>92.4</td>
<td>95</td>
<td>0.47</td>
<td>48</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>93</td>
<td>F</td>
<td>11300</td>
<td>22.5</td>
<td>92</td>
<td>0.46</td>
<td>170</td>
<td>26</td>
</tr>
<tr>
<td>5</td>
<td>99</td>
<td>F</td>
<td>6200</td>
<td>40.9</td>
<td>93</td>
<td>0.35</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td>73–271</td>
<td>5–16.2</td>
<td>80–100</td>
<td>0.40–0.50 (F); 0.42–0.52 (M)</td>
<td>150–590</td>
<td>4–45</td>
</tr>
</tbody>
</table>

1. MMA, methylmalonic acid; Hcy, homocysteine; MCV, mean corpuscular volume; Hct, hematocrit; ND, not done.
2. Severe paresthesia documented in the medical record for several years.
3. Several years of neurologic complaints with severe myelopathy, upper and lower extremity weakness, personality change, and positive Lhermitte sign.
4. These three subjects were the most vitamin B-12-deficient subjects in a cohort (n = 183) of nursing home patients.
with inborn errors of cobalamin metabolism. Thus, these elevations probably represent vitamin B-12 deficiency.

Megaloblastic anemia was found to be rare in two elderly cohorts with a $\approx 12\%$ prevalence of vitamin B-12 deficiency (1, 2). Mean corpuscular volume was high (100.6 and 100.5 fl) in only two of the seven most vitamin B-12–deficient subjects whose MMA values ranged from 2200 to 6820 nmol/L. A minor degree of anemia (hematocrit $\geq 0.36$) was present in four of the same subjects (1, 2).

Comorbidity complicates the recognition of the clinical manifestations of vitamin B-12 deficiency in the elderly. Diabetes mellitus, peripheral vascular disease, osteoarthritis, spinal stenosis, Alzheimer disease, and other dementias are common in the elderly and can cause paresthesias, sensory loss, gait disturbances, neuropathy, other leg pain syndromes, and cognitive loss. Several studies have addressed the prevalence of vitamin B-12 deficiency in dementia syndromes (1, 52, 58–64), particularly Alzheimer disease, and have also studied the benefits of treatment (1, 52, 62–64). One study suggested that delay in vitamin B-12 treatment may have been associated with lack of response of cognitive abnormalities (63). In another study, dementia did not appear to be related to vitamin B-12 deficiency and treatment did not benefit dementia (64), although the concentration of serum vitamin B-12 used to divide the subjects (110 pmol/L, or 150 pg/mL) was too low: deficient subjects would have been present in both the low and the normal groups. In a Netherlands cohort with dementia, only one patient of 19 treated with parenteral vitamin B-12 responded with improved cognitive functioning (62). Because vitamin B-12 deficiency was defined only as a vitamin B-12 concentration $< 150$ pmol/L ($< 200$ pg/mL) (62), however, the problem of false positives was not addressed.

MMA or tHcy concentrations have been measured in elderly patients with dementia or other neurologic or psychiatric abnormalities in several studies. The mean vitamin B-12 concentration was lower and the mean MMA concentration higher in a group of elderly patients from Denmark with Alzheimer dementia compared with patients with other dementias, patients with other mental disorders, or control subjects (60). The patients with Alzheimer dementia did not have the typical neurologic features of vitamin B-12 deficiency and only one had macrocytosis. In a cohort referred to a psychogeriatric department in Sweden, there was no difference in the mean concentration of tHcy in demented compared with nondemented seniors (61). Macrocytic anemia was rare in the subjects with low vitamin B-12 concentrations. Despite the fact that there was no correlation of tHcy with dementia, most subjects with vitamin B-12 $< 150$ pmol/L ($< 200$ pg/mL) had elevated tHcy, as did a significant number of subjects with vitamin B-12 concentrations $< 200$ pmol/L ($< 270$ pg/mL) (61). In another investigation, a battery of metabolic, vitamin B-12 absorption, neuropsychologic, and electrophysiology tests were evaluated in 13 elderly subjects with dementia and low serum vitamin B-12 concentrations before and after treatment (52). Abnormalities in MMA, tHcy, results of the deoxyuridine suppressive test, hemoglobin, mean corpuscular volume, neuropathy signs and symptoms, electroencephalograms, and visual evoked and somatosensory potentials improved in most of the subjects. However, results on neuropsychologic tests improved for only one demented patient (52).

Because both vitamin B-12 deficiency and Alzheimer disease and other dementias are common in the elderly population, it seems likely that many subjects will have combinations of disorders. It would take an astute clinician to determine what percentage of cognitive dysfunction in a specific individual could be attributed to only vitamin B-12 deficiency. Thus, it seems prudent to aggressively diagnose and treat vitamin B-12 deficiency. Similarly, painful paresthesia are common in diabetes mellitus, spinal disorders, and atherosclerotic peripheral vascular disease but the same elderly patients who have these disorders may also have vitamin B-12 deficiency. Although it would be desirable to treat vitamin B-12 deficiency, it is likely that the clinical response to treatment will be variable. The duration of prior symptoms was a major predictor of response in a study of well-defined patients with vitamin B-12 deficiency of the nervous system (45). It is likely that diagnosis would be delayed more in elderly subjects with multiple causes for similar neurologic symptoms than in younger, healthier patients and that the elderly subjects would thus be less likely to respond even if most of their signs and symptoms were actually due to vitamin B-12 deficiency. To answer some of the questions we have outlined about the sensitivity and specificity of the clinical manifestations of vitamin B-12 deficiency, the prevalence of megaloblastic anemia and neurologic symptoms compatible with vitamin B-12 deficiency should be determined in a large population survey such as the National Health and Nutrition Examination Survey (65) in subjects found to have elevated serum MMA concentrations.

**VITAMIN B-12 DEFICIENCY IS A MAJOR CAUSE OF HYPERHOMOCYSTEINEMIA IN THE ELDERLY**

There is mounting evidence that elevated homocysteine may be an independent risk factor for atherosclerotic and thrombotic vascular disease (10, 11), although there are no intervention studies proving this hypothesis. The underlying high prevalence of elevated MMA concentrations and vitamin B-12 deficiency in elderly populations has largely been overlooked in vascular disease studies despite mean ages of 55–60 y in many of the cohorts. We found that 60–66% of elderly subjects with elevated tHcy concentrations also had elevated MMA concentrations (66). These elevated MMA concentrations in association with hyperhomocysteinemia indicate subjects with vitamin B-12 deficiency only, probably combined vitamin B-12 and folate deficiency, or renal insufficiency. Comparing serum vitamin B-12 and folate concentrations is often not useful diagnostically because $\approx 33\%$ of elderly subjects have low or low-normal concentrations of both and another $\approx 33\%$ have normal concentrations of both (61). MMA was elevated in 66% of the Framingham subjects with serum folate concentrations $< 11$ nmol/L ($< 5$ ng/mL) as well as tHcy $> 16.2$ μmol/L (2, 66). MMA and tHcy concentrations are correlated in the elderly so that if hyperhomocysteinemic seniors are targeted for folate treatment, then undiagnosed vitamin B-12–deficient subjects will invariably be treated also (51, 66).

Few studies of elderly subjects with vascular disease have addressed the problem of the high prevalence of undiagnosed vitamin B-12 deficiency and the lack of sensitivity and specificity of the serum vitamin B-12 concentration. Recent publications addressing the serious methodologic problems associ-
ated with assaying serum and red blood cell folate only confuse these issues further (67, 68). Serum vitamin B-12 was not measured in subjects with myocardial infarction in the Physician’s Health Study although the advanced age (40–84 y) of some participants would have placed them at risk for vitamin B-12 deficiency (12, 69). This was a serious omission because serum folate and pyridoxal 5’-phosphate concentrations were not significantly lower in the case subjects, although there were more case than control subjects with tHcy values above the 95th percentile (69). In subjects from the Framingham Heart Study cohort, the prevalence of extracranial carotid stenosis was increased when tHcy was in the top quartile, which was correlated directly with plasma folate and pyridoxal 5’-phosphate and inversely with folate intake (15). However, a subgroup of this cohort was found to have a high prevalence of elevated MMA concentrations in combination with tHcy (2, 66). Vitamin B-12 deficiency probably played a greater role in the hyperhomocysteinemia in these subjects than was fully appreciated when only vitamin intake and serum vitamin concentrations were analyzed. At this point we do not know the age at which the prevalence of elevated MMA and vitamin B-12 deficiency starts to sharply increase. However, in one study MMA was elevated in 44% of hyperhomocysteinemic subjects (mean age: 58 y) with hyperlipidemia (14). In the Boston Heart Study, patients with a mean age of 58 y who had sustained a myocardial infarction were also found to have both higher MMA and higher tHcy concentrations (70).

This high prevalence of vitamin B-12 deficiency in older subjects with hyperhomocysteinemia raises several practical issues in designing intervention studies that would use folic acid treatment to lower tHcy in vascular disease patients. Megaloblastic anemia may remit when a vitamin B-12-deficient subject receives a large dose of folic acid, a phenomenon termed “masking of anemia.” The neurologic signs and symptoms of untreated vitamin B-12 deficiency can progress in such patients, however. There are few data available for determining a “safe” concentration of folate supplementation (71), although 1 mg is widely touted. The recognition that neurologic and hematologic severity are inversely related and that a significant subset (10–30%) of vitamin B-12-deficient subjects initially present with neurologic symptoms further confuses the issues (44, 45). It would be inappropriate in intervention studies to screen out those elderly subjects with elevated MMA in addition to elevated tHcy values because the remaining group would not be representative of the general population at risk for vascular disease. Also, the question must be raised as to whether it is ethical to treat known vitamin B-12-deficient subjects with a placebo. However, if vitamin B-12 is given to both placebo and intervention groups to satisfy ethical considerations, it is likely that the high tHcy concentrations due to vitamin B-12 deficiency will decrease significantly. Vitamin B-12 deficiency can also develop during long-term studies in a late middle-aged population.

Similar issues are raised by the food folate-fortification program now being implemented. Although the program is designed to prevent neural tube defects, some authors have speculated that increasing dietary folate will lower tHcy and possibly improve vascular health (11, 72). Oral folic acid in large doses of 10 mg/d will decrease tHcy concentrations in virtually every normal subject and in some subjects with unclear vitamin B-12 and folate status (54). In contrast, lower amounts of folate (5 mg) did not correct the hyperhomocysteinemia in 30% of treated subjects who may also have had mild renal insufficiency (14). Subjects with vascular disease and hyperhomocysteinemia generally have higher serum creatinine compared with control subjects (14, 16) and the benefit of smaller increases in folate intake has not been studied extensively in patients with renal insufficiency. Serum tHcy also remains high despite large daily folic acid supplements in subjects with frank renal failure (73). A high mean dietary intake of folate (300 μg) did not eliminate hyperhomocysteinemia in a recently studied elderly cohort (51) because all of the subjects with tHcy > 16.2 μmol/L also had elevated serum MMA as a result of vitamin B-12 deficiency or renal impairment. At this point there are not enough data to speculate whether small increases in dietary folate will significantly lower tHcy concentrations in the elderly.

WHAT DOSE OF ORAL VITAMIN B-12 WILL CORRECT DEFICIENCY IN THE ELDERLY?

Vitamin B-12 is readily available in foods of animal origin and is extensively stored and conserved via the enterohepatic circulation (74). There are multiple causes of vitamin B-12 deficiency in the elderly, including true pernicious anemia, atrophic gastritis causing food vitamin B-12 malabsorption, and previous gastric or other intestinal surgery (5, 52). The traditional treatment of pernicious anemia in the United States is injections of vitamin B-12. However, several studies in subjects with pernicious anemia showed that oral doses of 300–1000 μg are effective in raising serum vitamin B-12 concentrations and preventing clinical abnormalities (75–77). It is likely that similar doses of vitamin B-12 would be effective in elderly subjects with less complete malabsorption.

A major gap in our knowledge is the lowest quantity of oral vitamin B-12 that would correct elevated MMA concentrations in either all or most elderly subjects, including those with renal insufficiency. The mean serum vitamin B-12 concentration rose from 100 pmol/L (146 pg/mL) to 270 pmol/L (371 pg/mL) in elderly subjects in a geriatric ward in Belgium who received an oral solution containing 100 μg vitamin B-12/d for 30 d (78). The serum vitamin B-12 concentration was normalized in 88% of the patients studied after 1 mo. Neither MMA nor tHcy was measured in these subjects, but the marked rise in the serum vitamin B-12 concentration suggests that the dose was effective. Standard multivitamin pills available in the United States contain a much lower dose of vitamin B-12 than used in this study, usually < 10 μg. In the Framingham cohort, multivitamin use resulted in a lower prevalence of vitamin B-12 deficiency and elevated MMA and tHcy, but did not eliminate the risk (2). A similar decrease in mean tHcy and MMA was found in multivitamin supplement users in an elderly New Mexico cohort (51). However, the most vitamin B-12-deficient subject, with serum MMA concentration of 1300 nmol/L and tHcy concentration of 21.3 μmol/L, was taking a multivitamin containing 6 μg vitamin B-12 and 400 μg folic acid (51). It seems likely that an adequate oral vitamin B-12 supplementation amount for most elderly subjects would be > 6 but < 300 μg/d.

A further unanswered question is whether the vitamin B-12 added to breakfast cereals, liquid nutritional supplements, and
other highly processed foods is more bioavailable than the vitamin B-12 naturally protein-bound in animal foods. Another issue is whether dietary animal protein would cause a secondary binding of vitamin B-12, resulting in decreased absorption of supplemental vitamin B-12. Finally, a recent investigation in California suggests that pernicious anemia may affect 2% of the elderly (79): should supplemental vitamin B-12 be required to protect individuals with pernicious anemia as well as those with food vitamin B-12 malabsorption related to atrophic gastritis?

SUMMARY

Screening studies of elderly cohorts have revealed a high prevalence (up to 14%) of previously undiagnosed vitamin B-12 deficiency manifested by elevations in serum MMA or tHcy. These elevated metabolites can be readily corrected with parenteral vitamin B-12 supplementation. Hyperhomocysteinemia in the elderly is usually accompanied by elevated MMA concentrations and often other evidence of vitamin B-12 deficiency. However, clear-cut megaloblastic anemia and myelopathy or neuropathy are rare in elderly vitamin B-12-deficient subjects despite often high concentrations of MMA or tHcy. The actual prevalence of megaloblastic anemia or neurologic disorders in all subjects with vitamin B-12 deficiency is not known because selection bias favors the presentation of megaloblastic anemia. Therefore, clinical manifestations cannot be used as the only screening or treatment guide. Large amounts of oral vitamin B-12 (100–1000 μg/d) appear to be effective in increasing serum vitamin B-12 concentrations, but the small quantity of vitamin B-12 in most multivitamin preparations (6 μg) is not sufficient to correct elevated MMA concentrations in all elderly subjects. Further investigations need to be directed toward practical methods of screening for and treating vitamin B-12 deficiency in the millions of elderly persons at risk, especially because dietary folic acid will be increased in the near future as a result of the food folate-fortification program.

We thank Linda Farb, Bev Raab, and Paul Marcell for years of technical help. Pam Schillam, of the Colorado Department of Health, abstracted the medical records of the nursing home residents whose data are shown in Table 1. The authors and the University of Colorado and Columbia University hold patents relating to the use of methylmalonic acid, homocysteine, cystathionine, and methylocitrulline in the diagnosis and follow-up of vitamin B-12 and folate deficiency. A company has been formed at the University of Colorado to perform the assays.

REFERENCES


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