Effect of supplementation with cobalamin carried either by a milk product or a capsule in mildly cobalamin-deficient elderly Dutch persons

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ABSTRACT

Background: A high prevalence of cobalamin deficiency occurs in the elderly population, which may be treated orally or with injections. Little is known about the relative bioavailability of crystalline cobalamin added to food products.

Objective: The objective was to assess the effect of supplementation with 1000 μg crystalline cobalamin, carried either by a milk product or a capsule, on cobalamin status in mildly cobalamin-deficient elderly Dutch persons.

Design: Two double-blind randomized controlled intervention studies, each covering a 12-wk supplementation period, were carried out in parallel. Mildly cobalamin-deficient elderly persons (n = 112) were separately recruited for the milk and capsule trials. Mild cobalamin deficiency was defined as a cobalamin concentration between 100 and 300 pmol/L and a plasma methylmalonic acid (MMA) concentration ≥0.30 μmol/L. Allocation to the placebo or cobalamin carrier was carried out independently in both trials.

Results: In the fortified-milk group, the mean (± SD) increase in serum cobalamin was 250 ± 96 pmol/L, the median (5th and 95th percentiles) decrease in plasma MMA was 0.19 (−0.76, −0.04) μmol/L, and the median decrease in plasma homocysteine was 4.0 (−7.3, 3.0) μmol/L. All changes were significantly different from those in the placebo milk group (P < 0.01). Likewise, in the cobalamin-capsule group, the mean increase in serum cobalamin was 281 ± 136 pmol/L, the median decrease in plasma MMA was 0.18 (−2.95, 0.14) μmol/L, and the median decrease in plasma homocysteine was 1.8 (−10.6, 2.4) μmol/L; all changes were significantly different from those in the placebo capsule group (P < 0.01). No significant differences were observed between the fortified-milk and capsule groups (P > 0.40).

Conclusion: Crystalline cobalamin added to milk is an effective alternative to cobalamin capsules for improving cobalamin status.

KEY WORDS Vitamin B-12, elderly people, fortified milk, oral cobalamin treatment

INTRODUCTION

Many studies have shown a high prevalence of cobalamin deficiency in elderly populations, ranging from 12% to 40% (1–4). This deficiency may cause neuropsychiatric damage, including cognitive impairment, and hematologic abnormalities, even in cases of mild cobalamin deficiency (1, 2, 5). Therefore, cobalamin deficiency in old age is considered to be a substantial problem for public health, which needs to be managed adequately.

Different indicators and cutoffs have been used to define mild cobalamin deficiency. Currently, plasma methylmalonic acid (MMA) and homocysteine concentrations are used along with serum cobalamin concentrations to assess cobalamin deficiency. However, homocysteine is also elevated in folate and vitamin B-6 deficiency. Therefore, MMA is the preferred indicator because of its higher sensitivity and specificity (6).

High doses of cobalamin, eg, from intramuscular injections or oral supplements, are needed to treat cobalamin deficiency (7–9). Unfortunately, injections may be painful and are difficult to administer in persons with a tendency to bleed or who are thin. Moreover, injections are costly when given by health professionals (10, 11). Supplements of 1000 μg vitamin B-12/d may be an alternative to injections, because only high doses produce successful long-term results, as indicated by Elia (10) and by Lane and Rojas-Fernandez (12). Such high doses cannot be derived from the diet alone, which provides an average of ≈5.5 μg/d (13). This amount (4) meets the American and Dutch recommended daily allowance (2.4 and 2.8 μg/d, respectively). A dose of 1000 μg cobalamin/d is generally considered to be safe. A safe upper level for cobalamin intake has not yet been set, but a supplemental intake of 2000 μg/d is considered a safe upper limit (14). No treatment-related adverse events after doses of 1000-2000 μg/d for periods ranging from 6 wk to 12 mo have been reported (8, 9, 15). Although supplements may be advised, an extra pill every day may affect compliance with regular medication use, especially in the elderly, who already use a lot of medicines daily (16). An alternative would be to add cobalamin to the food. Such fortified foods may have other benefits, such as providing energy and other nutrients that may be low in the diets of elderly persons (17).
In light of cereal fortification with folate, which has been mandatory in the United States since January of 1998, food fortification with cobalamin has gained interest (18, 19) because folate fortification alone may lead to an increased risk of masked cobalamin deficiency, particularly in the elderly (20–22). However, little is known about the bioavailability of crystalline cobalamin that has been added to a food product. Only Russell et al (23) have studied the absorption of 0.25 μg cobalamin from water (55%), milk (65%), and bread (55%) in non-cobalamin-deficient older adults. The effect that high doses of crystalline cobalamin in fortified foods would have on the cobalamin status of elderly Dutch people with a mild cobalamin deficiency is not yet clear. Therefore, the aim of our study was to assess the effect of supplementation with 1000 μg crystalline cobalamin for 12 wk, carried either by a milk product or by a capsule, on cobalamin status in mildly deficient elderly Dutch persons compared with that in a placebo group.

SUBJECTS AND METHODS

We carried out 2 double-blind, independent, randomized controlled trials, each of which lasted 12 wk. In one of these trials, a milk product carried the high cobalamin dose; in the other trial, a capsule carried it. In both trials, a placebo group consumed either a milk drink or a placebo capsule without cobalamin. Neither the subjects nor the investigators knew which supplements served as the placebo or intervention. The 2 capsule groups were part of a larger study in which 3 capsule groups were studied: placebo, vitamin B-12, or vitamin B-12 plus folic acid. The improvement in cobalamin status was assessed after 12 wk on the basis of the change in plasma MMA and serum cobalamin concentrations, which were the primary outcome measures. Plasma homocysteine and red blood cell (RBC) folate were evaluated as secondary outcome measures.

Subjects

For both trials, men and women aged ≥70 y were enrolled voluntarily by mail with the consent of the staff of their sheltered housing residence. Subjects with a history of cobalamin deficiency, of high-cobalamin (>50 μg/d) or -folate (>200 μg/d) supplementation or injections, gastrointestinal surgery, renal dysfunction (serum creatinine >120 μmol/L), anemia, or cancer were excluded on the basis of self-reports. Only subjects with mild cobalamin deficiency were included in the trials; their serum cobalamin concentrations ranged from 100 to 300 pmol/L (6) and their plasma MMA concentrations were ≥0.30 μmol/L (1); these variables were checked in a blood sample drawn ≥1 h after a light breakfast was eaten. All of the subjects gave their written informed consent. The medical ethics committee of Wageningen University approved the research protocols.

Study design

Before the trials began, all eligible subjects participated in a 2-wk run-in period in which they received a placebo milk drink or capsule. The subjects were matched by sex, MMA concentration, and age for random distribution of the placebo or the cobalamin carrier. In the matching procedure, priority was given to MMA. In most cases, the MMA concentration of the matched pairs did not differ by >0.02 μmol/L. Consequently, an age difference of 10 y occurred within one matched pair. Allocation of the placebo or cobalamin carrier was carried out independently in both trials. After the run-in period, baseline blood samples and anthropometric data were collected after the subjects fasted overnight (no food eaten after 20:00); the subjects were allowed a prescribed light breakfast (toast, bread, jam or other sweet spread, cheese, yogurt, milk, coffee or tea; no peanut butter, juice, meat, or products rich in vitamin B-12 were allowed) the next morning until 1 h before blood was drawn. After the blood samples were collected, the subjects received either the placebo or the cobalamin carrier. The milk was provided in 300-mL containers along with 125-mL cups. Every morning, the subjects had to consume 125 mL milk. The capsules were provided in medicine boxes on which the days and week were indicated, so each box contained 7 capsules. One capsule was taken each day, and each subject had a diary in which he or she indicated whether the milk or capsule was consumed. Compliance was assessed by reviewing the diary contents and by counting any remaining capsules. The diary of the subjects who received the milk drink contained an additional column for reporting, after every 4 d, approximately how much milk was left in the container. We calculated noncompliance as the amount of milk that was not consumed or the number of capsules that were not consumed. In both trials, compliance (%) was calculated by using the following formula:

\[
\text{Compliance} = 100 - \left( \frac{\text{noncompliance}}{\text{total amount of milk or capsules to be consumed}} \right) \times 100 \quad (1)
\]

During the 12-wk period, the participants were asked to maintain their regular diet and also to avoid consumption of cobalamin-rich food products. A list of products rich in cobalamin, mainly liver products, was provided to participants of the milk trial. After 12 wk, a second blood sample was collected from each subject, again with allowance for a light breakfast until 1 h before blood sampling.

Cobalamin carrier

The milk was manufactured by NIZO food research (Ede, Netherlands). Either 8000 μg/L of crystalline cyanocobalamin (fortified product) or 25 μg/L carmine extract with E-number E120 (placebo product) was added to semi-skim milk. Subsequently the products were homogenized at 150/30 bar, sterilized at 140 °C for 5 s, and aseptically filled in 500-mL polyethylene containers. The containers were closed with an aluminum seal. The carmine extract was added to the placebo milk to achieve a color similar to that of the fortified milk. Carmine extract is known not to have any flavor characteristics. Therefore, no differences in flavor and color between the 2 milk products were observed. The energy content of both milk types was 194 kJ/100 mL. During the study, a cobalamin assay was performed on each milk type. The cobalamin-fortified milk contained 7000 μg/L, whereas the placebo milk contained 3.7 μg cobalamin/L.

The capsules were manufactured by Dutch BioFarmaceutics (Helmond, Netherlands) and contained AVICEL PH102 as a filler (placebo; Medipulp GmbH, Germany) and 1000 μg crystalline cyanocobalamin. The capsules had identical appearances, smells, and tastes. A cobalamin assay of several of the capsules was performed; the mean concentration was 936 ± 34 μg. The milk containers and the capsules were coded so that neither the investigator nor the participants were aware of the contents.
Laboratory methods

Serum cobalamin, RBC folate, plasma MMA, and plasma homocysteine were measured at baseline and after 12 wk. Blood hemoglobin, hematocrit, mean cell volume (MCV), and polymorphonuclear hypersegmentation were measured at baseline.

Cobalamin and RBC folate were analyzed on the day of collection. Blood samples for cobalamin measurement were placed in the dark immediately after collection. Blood samples for measurement of RBC folate were stored at 7 °C within 4 h after blood collection. An automated chemiluminescent immunoassay analyzer (Access 2; Beckman Coulter, Mijdrecht, Netherlands) was used to measure serum cobalamin and RBC folate concentrations. The interassay CV was 6.3% for the cobalamin assay and 5.9% for the RBC folate assay (Stichting Huisartsenlaboratorium Oost, Velp, Netherlands).

Hemoglobin, hematocrit, and MCV were measured with a Beckman-Coulter hematology analyzer. The reference value for low hemoglobin is <7.5 mmol/L, for low hematocrit is <0.38 L/L, and for macrocytosis is >100 fl (24). Polymorphonuclear hypersegmentation was checked by microscopy and defined as hypersegmentation when five-lobed neutrophils/four-lobed neutrophils is ≥ 0.17 (25). Blood samples for measurement of plasma MMA and homocysteine were collected in EDTA-treated tubes and placed immediately in ice water. Plasma was separated by centrifugation (2600 × g for 10 min at 4 °C) within 30 min and was stored at −20 °C until analyzed further. Plasma MMA concentrations were measured with the use of a liquid chromatography mass spectrometry method (LC-MS-MS), with a CV of 5% (personal communication; University Medical Center, St Radboud, Nijmegen, Netherlands, 2003). The total plasma homocysteine concentration was measured by HPLC with fluorimetric detection (CV 7%) at the Division of Human Nutrition, Wageningen University, Wageningen, Netherlands.

Statistical analysis

When necessary, baseline data were log transformed to normalize the distribution, and geometric means were calculated. Baseline characteristics between treatment groups were compared by one-way analysis of variance (ANOVA) and chi-square analysis for categorical variables. Levene’s test was used to test for equal variances. Compliance between groups was compared with the Kruskal-Wallis test.

Changes from baseline to the end of the 12-wk study were analyzed with a paired Student’s t test or with Wilcoxon’s signed-rank test. Differences in the mean change in cobalamin concentration between groups were analyzed with an independent-sample Student’s t test. Mean changes in MMA, homocysteine, and RBC folate concentrations were compared between the cobalamin groups with a Mann-Whitney U test. A Mann-Whitney U test was used because it was not possible to normalize the skewed changes. Mann-Whitney-U test and Student’s t test were also used to analyze whether there was a difference in effect between cobalamin-fortified milk and cobalamin capsules, and the results were corroborated by 2-factor (cobalamin × carrier) ANOVA. Bonferroni corrections were applied to adjust the P values for multiple comparisons (each mean change compared with 2 other mean changes). Although there were technically 6 possible comparisons between the 4 groups, only 3 were of theoretical interest: 1) cobalamin-placebo, milk group; 2) cobalamin-placebo, capsule group; and 3) milk-capsule, cobalamin intervention. Therefore, we corrected for 3 tests.

The nature of our data rendered the 2-factor ANOVA inappropriate; therefore, it was only used to illustrate and strengthen the findings of the Mann-Whitney U test and Student’s t test. Data were analyzed by using SAS system release 8.0 (SAS Institute Inc, Cary, NC). In all analyses, a P value of 0.05 was considered significant.

RESULTS

The flow of participant selection in both randomized trials is shown in Figure 1. Of the total number of elderly subjects who were interested in participating in one of the studies (n = 1079), 615 were screened for cobalamin deficiency. Others had second thoughts (n = 322) or were excluded on the basis of the exclusion criteria in the health questionnaire (n = 142). After screening, 113 persons were identified as being mildly cobalamin deficient (18% of the screened population). These 113 subjects were randomly assigned to one of the treatment groups, which consisted of a cobalamin carrier or a placebo. Seven persons subsequently withdrew for health reasons. Compliance was not significantly different between treatment groups (P = 0.09): 90% of subjects consumed >90% of their supplements.

Baseline hemoglobin, hematocrit, and MCV values were not significantly different between the treatment groups. Only 3 subjects had low hemoglobin, 9 subjects had low hematocrit, and 1 subject had macrocytosis. Polymorphonuclear hypersegmentation was found in 85% of the subjects, and these subjects were equally distributed between the treatment groups, except for the cobalamin-capsule group—59% of the subjects were diagnosed with hypersegmentation (Table 1).

There were no significant differences in any of the baseline characteristics between the treatment groups, most probably because of successful randomization (Table 1 and Table 2). The cobalamin status of one subject in the fortified-milk group improved in the period between screening and baseline measurements, so this subject could no longer be defined as cobalamin deficient at baseline and was therefore excluded from further analyses.

In the cobalamin-carrier groups, all biochemical changes from baseline to 12 wk were significant, except for RBC folate concentrations in the cobalamin-capsule group (P = 0.10) (Table 2). There were no significant biochemical changes in the placebo groups, except for an increase in MMA concentration in the milk group (P = 0.04). A comparison of changes induced by the milk-cobalamin carriers and by the milk-placebo group showed significant differences, whereas MMA and homocysteine concentrations decreased and cobalamin and RBC folate concentrations increased in the milk-cobalamin group. A comparison of changes induced by the capsule-cobalamin carrier and the placebo group also showed significant differences, whereas the capsule-cobalamin group showed decreases in MMA and homocysteine concentrations and increases in cobalamin concentrations. RBC folate concentrations also increased, but not significantly so.

No significant differences in effect were observed between the cobalamin-fortified milk and the cobalamin capsules. Changes in cobalamin, MMA, homocysteine, and RBC folate were not significantly different between the intervention groups (P > 0.40).
The cobalamin-fortified milk and capsules normalized the cobalamin status of all but 5 subjects. In 2 subjects in the milk trial, the cobalamin concentration did not reach 300 pmol/L. These 2 subjects had low baseline cobalamin concentrations (84 and 101 pmol/L). The MMA concentration of another subject in the milk trial decreased from 0.71 to 0.33 μmol/L. In the capsule trial, 2 subjects had minor improvements (59 and 42 pmol/L) in cobalamin concentrations; these subjects had baseline concentrations of 102 and 143 pmol/L, respectively. More importantly, the MMA concentration in the subject with a cobalamin concentration of 143 pmol/L increased from 0.46 μmol/L at baseline to 0.60 μmol/L after 12 wk. However, the compliance of this subject could not be checked because his diary and medicine boxes were not provided.

**DISCUSSION**

We performed a double-blind, placebo-controlled supplementation study in elderly mildly cobalamin deficient subjects who received 1000 μg crystalline cobalamin/d carried either by milk or a capsule. After 12 wk, the improvement in cobalamin status from 0.46 μmol/L at baseline to 0.60 μmol/L after 12 wk. However, the compliance of this subject could not be checked because his diary and medicine boxes were not provided.

**TABLE 1**

Baseline characteristics of the mildly cobalamin-deficient Dutch participants, by treatment group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Milk trial</th>
<th>Placebo</th>
<th>Capsule trial</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>81 ± 5.6$^2$</td>
<td>82 ± 3.7</td>
<td>82 ± 5.4</td>
<td>82 ± 4.7$^7$</td>
</tr>
<tr>
<td>Women [n (%)]</td>
<td>13 (68)</td>
<td>13 (68)</td>
<td>15 (79)</td>
<td>18 (75)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.70 ± 0.11</td>
<td>1.65 ± 0.09</td>
<td>1.65 ± 0.11$^6$</td>
<td>1.65 ± 0.10$^7$</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.4 ± 11.8</td>
<td>70.5 ± 11.4</td>
<td>70.3 ± 11.2$^6$</td>
<td>74.2 ± 10.3$^7$</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>8.8 ± 0.5</td>
<td>8.7 ± 1.0</td>
<td>8.4 ± 0.9$^3$</td>
<td>8.9 ± 0.6</td>
</tr>
<tr>
<td>Hematocrit (L/L)</td>
<td>0.43 ± 0.03</td>
<td>0.42 ± 0.05</td>
<td>0.41 ± 0.05$^5$</td>
<td>0.43 ± 0.04</td>
</tr>
<tr>
<td>MCV (fL)</td>
<td>91 ± 2.6</td>
<td>92 ± 4.4</td>
<td>91 ± 3.5</td>
<td>91 ± 5.7</td>
</tr>
<tr>
<td>Percentage hypersegmentation (%)</td>
<td>100</td>
<td>95</td>
<td>59</td>
<td>83</td>
</tr>
</tbody>
</table>

$^1$ MCV, mean cell volume. There were no significant differences between the groups by one-factor ANOVA for continuous variables and by chi-square analysis for categorical variables.

$^2$ x ± SD (all such values).

$^6$ n = 22.

$^7$ n = 18.

$^8$ n = 17.
TABLE 2
Mean (±SD) cobalamin, methylmalonic acid (MMA), homocysteine (Hcy), and red blood cell (RBC) folate concentrations in mildly cobalamin deficient participants by treatment group at baseline and after 12 wk

<table>
<thead>
<tr>
<th>Blood variable</th>
<th>Cobalamin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline (n = 19)</td>
<td>Week 12 (n = 19)</td>
</tr>
<tr>
<td>Cobalamin (pmol/L)</td>
<td>182 ± 60†</td>
<td>432 ± 134‡</td>
</tr>
<tr>
<td>MMA (µmol/L)</td>
<td>0.39 (0.22, 0.96)§</td>
<td>0.22 (0.15, 0.33)§</td>
</tr>
<tr>
<td>Hcy (µmol/L)</td>
<td>16.0 (8.3, 24.7)</td>
<td>11.9 (8.1, 18.6)</td>
</tr>
<tr>
<td>RBC folate (µmol/L)</td>
<td>539 (297, 1078)</td>
<td>664 (412, 1037)</td>
</tr>
<tr>
<td>Capsule trial</td>
<td>Cobalamin (µmol/L)</td>
<td>171 ± 51</td>
</tr>
<tr>
<td>MMA (µmol/L)</td>
<td>0.38 (0.25, 3.24)</td>
<td>0.23 (0.14, 0.60)</td>
</tr>
<tr>
<td>Hcy (µmol/L)</td>
<td>17.6 (10.1, 26.5)</td>
<td>13.4 (10.4, 23.2)</td>
</tr>
<tr>
<td>RBC folate (µmol/L)</td>
<td>600 (385, 872)</td>
<td>666 (408, 951)</td>
</tr>
</tbody>
</table>

† There were no significant differences between the 4 groups.
‡ The biochemical changes after intervention were not significantly different between the cobalamin carriers. Student’s t test: cobalamin, P = 0.41.
§ Mann-Whitney U test: MMA, P = 0.80; Hcy, P = 0.54; RBC folate, P = 0.41. Bonferroni correction did not change the significance of the results.
* Reflects the comparison of changes between the cobalamin and placebo groups for each carrier by Student’s t test or the Mann-Whitney U test after Bonferroni correction.
† † ± SD (all such values).
‡ ‡ Significantly different from baseline, P < 0.05 (paired Student’s t test for cobalamin and Wilcoxon’s signed-rank test for MMA, Hcy, and RBC folate).
§ Median; 5th and 95th percentiles in parentheses (all such values).
* n = 24.
× Hcy measurements for 2 to 3 samples per group were not available because of inadequate amounts of plasma.

was not significantly different between intervention groups. Therefore, we conclude that high doses of crystalline cobalamin added to milk are as easily absorbed as are high doses of crystalline cobalamin in capsules. Our subjects were considered compliant in consuming the fortified milk drinks and the capsules. Cobalamin status improved in all subjects who received a cobalamin carrier, except for the one subject whose MMA concentration increased. However, the compliance of this subject was questionable. Exclusion of this subject did not change the conclusions. In 4 other subjects, instead of normalizing, the cobalamin status improved. We presume that, for 3 of these subjects, the supplementation period was too short to normalize vitamin B-12 status. For the fourth subject, it was not clear why the cobalamin and MMA concentrations did not improve sufficiently, because favorable changes in RBC and homocysteine concentration occurred. We do not expect that this subject’s cobalamin status would have improved more if he had been supplemented with both cobalamin and folate instead of with cobalamin alone. For all other subjects, complementary folate supplementation could have lowered homocysteine concentrations to a larger extent (26, 27), although cobalamin supplementation alone appeared to be sufficient to normalize the cobalamin status in this study.

Our cutoffs for defining mild cobalamin deficiency were deliberately chosen on the basis of published data and laboratory experience, but are debatable because there are no universally accepted limits for defining mild cobalamin deficiency. The lower limit for normal serum cobalamin ranges from 150 to 300 pmol/L (1, 2, 4, 6), whereas the upper limit for normal plasma MMA ranges from 0.27 to 0.38 µmol/L (1–4). This variation reflects differences in analytic methods, in statistical analyses, and in the composition of the control populations. In future studies, holo-transcobalamin may be used as an additional indicator of true cobalamin deficiency (28), because early changes in blood cobalamin homeostasis may be detected (29). Still, universally accepted cutoffs for holotranscobalamin need to be defined for cobalamin deficiency. The high prevalence of hypersegmentation (85%) is in line with the vitamin B-12 deficiency for which it was screened. Neutrophil hypersegmentation has been suggested to indicate vitamin B-12 or folate deficiency (30). It can be routinely performed and may be more convenient when assays for vitamin B-12 status are not available.

The cause of cobalamin deficiency was not assessed in this study, because we expected all mildly cobalamin deficient elderly people to benefit from the crystalline cobalamin dose. This improvement in cobalamin status cannot give an idea of the cause of vitamin B-12 deficiency, eg, pernicious anemia or malabsorption of cobalamin in food, because such an improvement would occur in all cases. Although the regular pathway of absorption (with intrinsic factor) may be disturbed in perniciously anemic subjects, all persons will be absorbed by passive diffusion (11, 31). Because only 1–1.9% of elderly persons have pernicious anemia (1, 32, 33), and given the low prevalence of low hemoglobin and hematocrit values in our subjects, pernicious anemia was not present or was only minimally present in the subjects in this study. Other causes of cobalamin deficiency could be deficient dietary intake or malabsorption of food-bound cobalamin. A study of 103 elderly Dutch subjects showed that only 6% had low dietary intakes (4). Therefore, it is more likely that most of our subjects had food-bound cobalamin malabsorption. Causes of food-cobalamin malabsorption are atrophic gastritis (which may cause a decrease in gastric acidity or hypochlorhydria), Helicobacter pylori infection, or gastric infection by anaerobic bacteria (34, 35).

A few studies assessed changes in biochemical variables or studied the absorption (or matrix) of cobalamin after supplementation with radioactive crystalline cobalamin. As expected from...
these biochemical studies in elderly people (7–9, 36), the cobalamin status improved after 12 wk of supplementation with cobalamin capsules. All studies that assessed the absorption of crystalline cobalamin used very low doses. Therefore, sufficient passive diffusion was minor. It appeared that the carrier of cobalamin was important because the absorption of 0.56 μg crystalline cobalamin was inhibited by egg white and egg yolk, when measured with fecal and urinary excretion in a healthy volunteer (37). In a more recent study, 0.25 μg crystalline cobalamin was inhibited by egg white and egg yolk, when measured with fecal and urinary excretion in a healthy volunteer (37).

Additional studies are required to assess whether lower-dose cobalamin-fortified foods may prevent cobalamin deficiency, especially in the elderly.

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