Effects of folic acid and combinations of folic acid and vitamin B-12 on plasma homocysteine concentrations in healthy, young women[1,2]

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ABSTRACT

Background: Elevated plasma homocysteine concentrations are considered to be a risk factor for vascular disease and fetal malformations such as neural tube defects. Recent studies have shown that plasma homocysteine can be lowered by folic acid in amounts corresponding to 1–2 times the recommended dietary allowance. Preliminary evidence indicates that vitamin B-12 may be beneficial when included in supplements or in a food-fortification regimen together with folic acid.

Objective: We aimed to compare the homocysteine-lowering potential of a folic acid supplement with that of 2 supplements containing different doses of vitamin B-12 in addition to folic acid.

Design: Female volunteers of childbearing age (n = 150) received a placebo for 4 wk followed by a 4-wk treatment with either 400 μg folic acid, 400 μg folic acid + 6 μg vitamin B-12, or 400 μg folic acid + 400 μg vitamin B-12.

Results: Significant reductions ($P < 0.001$) in plasma homocysteine were observed in all groups receiving vitamin treatment. The effect observed with the combination of folic acid + 400 μg vitamin B-12 (total homocysteine, −18%) was significantly larger than that with a supplement containing folic acid alone (total homocysteine, −11%) ($P < 0.05$). Folic acid in combination with a low vitamin B-12 dose (6 μg) affected homocysteine as well (−15%).

Conclusions: These results suggest that the addition of vitamin B-12 to folic acid supplements or enriched foods maximizes the reduction of homocysteine and may thus increase the benefits of the proposed measures in the prevention of vascular disease and neural tube defects. *Am J Clin Nutr* 1998;68:1104–10.

KEY WORDS Folic acid, vitamin B-12, supplementation, homocysteine, neural tube defect, cardiovascular disease, women

INTRODUCTION

Homocysteine is being scrutinized as independent risk factor for coronary, cerebral, and peripheral vascular diseases. Most case-control studies and several, though not all, prospective studies have confirmed such an association over a wide range of plasma total homocysteine (tHcy) concentrations (1–4).

In the absence of vitamin B-6 or vitamin B-12 deficiency or genetic defects in non-folate-dependent enzymes, folic acid intervention lowers plasma tHcy concentrations. This has been observed even when presupplementation plasma folate concentrations were well within the range of values currently accepted as reflecting adequate status (5, 6). In several studies, daily folic acid administration in high (pharmacologic) doses of 0.5 (7) to 10 mg (8) resulted in significant reductions in plasma tHcy. However, for both sexes, additional folic acid intakes of 200–400 μg/d, corresponding to 1–2 times the recommended dietary allowance of 400 μg dietary folate equivalents (9), seem to be sufficient to lower plasma tHcy concentrations (5, 6, 10). Indirect evidence for the protective effect of low plasma tHcy concentrations comes from a recent prospective study linking high intakes of folate to a considerably diminished risk for coronary artery disease in 80 082 US nurses (11). Besides an involvement in the pathogenesis of vascular disease, maternal tHcy concentrations may further play a role in the etiology of fetal malformations such as neural tube defects (NTDs) (12–14).

As of January 1, 1998, the US Food and Drug Administration ruled that the fortification of grain and grain products with folic acid be mandatory to increase folic acid intakes and contribute to the prevention of NTDs (15). However, it has been suggested that vitamin B-12 be added to foods as well or that supplements be offered containing both folic acid and vitamin B-12 (12, 16, 17). The rationale for this proposition is that the sole addition of folic acid may mask pernicious anemia resulting from vitamin B-12 deficiency, which may slowly lead to irreversible nerve damage. Further support for this proposition is that both folic acid and vitamin B-12 are cofactors of methionine synthase, the enzyme catalyzing the formation of methionine from homocysteine. A defect in this enzyme, also resulting in elevated tHcy concentrations, was proposed to be the cause for some (although not all) NTDs.

The present study aimed to determine whether the addition of vitamin B-12 to a folic acid supplementation regimen recommended for women capable of becoming pregnant (9) potentiated the tHcy-lowering capacity of this regimen. Two different

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doses of vitamin B-12 were chosen to explore whether there was a dose-response relation with increasing vitamin B-12 dose. The low dose was approximately double the recommended dietary allowance of 2.4 μg/d (9) and reflects an amount frequently contained in vitamin supplements for adults (18). The high pharmacologic dose of vitamin B-12 takes into account the greatly reduced absorption rate of vitamin B-12 from high doses after saturation of the active absorption pathway (19). Women of childbearing age were chosen as the target population group because they may especially benefit from tHcy reduction.

SUBJECTS AND METHODS

The study was approved by the Ethical Committee of the University Hospital of Bonn. After a washout phase of 4 wk, 156 female participants aged 20–34 y received a placebo daily during the first 4 wk of the study. For the next 4 wk, the volunteers were randomly assigned to one of the following treatment groups: group A, 400 μg folic acid/d; group B, 400 μg folic acid + 6 μg vitamin B-12/d; and group C, 400 μg folic acid + 400 μg vitamin B-12/d. The vitamin capsules were specially prepared by Allpack (Schorndorf, Germany) with synthetic folic acid (pteroylmonoglutamic acid) from Takeda (Osaka, Japan) and vitamin B-12 (cyanocobalamin) from Merck (Darmstadt, Germany). Placebo and vitamin capsules were identical in appearance as the result of a colored gelatin cover so that the participants were not aware of the identity of the capsules. Capsules were provided in excess and participants were asked to return the remaining capsules after each 4-wk period to enable pill counting as a measure of compliance.

At the beginning of the washout phase, all subjects were instructed to continue their usual dietary habits for the duration of the study but to refrain from intake of other vitamin supplements or foods enriched with vitamins. Six participants opted to withdraw during the study; the 150 participants completing the study were included in the statistical analysis.

After subjects had fasted overnight, blood was drawn from each participant at the start of the study (week 0), after the placebo period (week 4), and after the treatment period (week 8). Blood was immediately cooled on ice and centrifuged within 15 min at 2000 × *g* and 4°C for 10 min. Plasma was stored at −20°C until analyzed.

Laboratory investigations

All samples for each participant were analyzed within one run to minimize measurement errors. EDTA-treated plasma was analyzed for tHcy by HPLC with fluorescence detection according to the method described by Araki and Sako (20) and Vester and Rasmussen (21) with minor modifications. The CVs for this assay were as follows: within-assay variation <5.6% and between-assay variation <5.7%. Folate and vitamin B-12 were measured in heparin-treated plasma with commercially available chemiluminescence kits (Chiron Diagnostics, Fernwald, Germany; within-assay CV <4.6% and <6.5%, respectively, and between-assay CV <13.0% and <9.1%, respectively). For the measurement of red blood cell (RBC) folate, the same chemiluminescence kit as for plasma folate was used (within-assay CV <10.7%, between-assay CV <13.1%). Hemolysis for this assay was achieved by incubating whole blood with 0.2% ascorbic acid at room temperature for 90 min before freezing the mixture according to the directions of the manufacturer of the kit. The assays for tHcy, folate, and vitamin B-12 were validated externally through participation in national and international interlaboratory comparisons (for tHcy: European External Quality Assurance Scheme for homocysteine in serum; for the vitamins: ringtest of the German Society for Clinical Chemistry). Vitamin B-6 was measured as pyridoxal-*P* (PLP) by HPLC (within-assay CV <2.3%, between-assay CV <5.9%) (22). All samples were analyzed in duplicate.

Statistical analysis

Because of positively skewed distributions, the natural logarithms of tHcy, folate, RBC folate, vitamin B-12, and PLP were used in all analyses as continuous variables. Therefore, besides presentation of arithmetic means, geometric means for these variables are given. The treatment groups were compared with respect to body mass index (BMI), plasma tHcy, folate, RBC folate, vitamin B-12, and PLP by means of parametric models [paired *t* test for within-subject comparisons and analysis of variance (ANOVA) for between-subject comparisons]. The primary analysis variable was the change in a plasma index after 4 wk of vitamin treatment. This change was expressed as the ratio of the concentration at week 8 to that at week 4, and a one-way ANOVA model was fitted to the ln-transformed ratio including a treatment effect. To account for the influence of tHcy and vitamin concentrations before treatment on the change in tHcy, these parameters were also included in the ANOVA as covariates. Post hoc tests used the Scheffe test. The age of the groups was compared by using a Kruskal-Wallis one-way ANOVA because a skewed distribution of the data remained after logarithmic transformation. Differences in proportions between the groups were tested by using a paired chi-square test. Correlation analysis used logarithmically transformed variables for calculation of Pearson's correlation coefficients. Differences were considered significant at $P < 0.05$; all *P* values are two-tailed. Data analyses were performed with the statistical program SPSS (version 6.1.3; SPSS Inc, Chicago).

RESULTS

The demographic characteristics of the study participants are summarized in **Table 1**. No significant differences were observed among groups with respect to age, BMI, use of oral contraceptives, or prevalence of smoking. Previous use of B vitamin supplements before the washout phase, which included regular intake of supplements containing vitamin B-6, vitamin B-12, or folic acid, was also not significantly different among groups. An estimation of compliance with intake of the capsules was possible for 146 of 150 participants (97.3%). Good compliance, defined as intake of ≥6 capsules/wk, was noted for all groups, ranging from 98.0% in group A to 100% in groups B and C.

Total homocysteine

At week 0 participants were normohomocysteinemic, with concentrations ranging from 3.5 to 14.3 μmol/L; the geometric mean value of all groups combined was 7.6 μmol/L. tHcy concentrations in plasma correlated inversely with concentrations of folate and vitamin B-12 in plasma ($r = -0.2828$, $P < 0.001$, and $r = -0.3774$, $P < 0.001$, respectively), but not with vitamin B-6 (PLP) ($r = -0.0771$, $P = 0.3$). The association with RBC folate (computed from measurements at week 4) was weaker ($r = -0.1752$, $P = 0.03$) than that observed with plasma folate at week 0.

TABLE 1
Demographic characteristics of the study participants[1]

Group	Group A ($n = 51$)	Group B ($n = 49$)	Group C ($n = 50$)
Age (y)	24.9 ± 3.5	24.0 ± 1.9	23.5 ± 2.1
BMI (kg/m^2)	20.9 ± 1.8	21.4 ± 2.2	21.3 ± 2.5
Use of OC (%)	58.8	55.1	54.0
Smoking (%)	9.8	14.3	22.0
Previous B vitamin supplementation (%)	25.5	22.4	18.0

[1] $\bar{x}$ ± SD or proportions. Group A received 400 μg folic acid/d, group B received 400 μg folic acid + 6 μg vitamin B-12/d, and group C received 400 μg folic acid + 400 μg vitamin B-12/d. The 3 groups did not differ significantly with respect to age ($P > 0.05$, Kruskal-Wallis ANOVA), BMI ($P > 0.05$, ANOVA), or prevalence of use of oral contraceptives (OC), smoking, and previous B vitamin supplementation ($P > 0.05$, chi-square test).

After 4 wk of placebo treatment, the geometric mean tHcy concentration of all study subjects increased slightly but significantly by a mean value of 0.28 μmol/L ($P < 0.01$). A subgroup analysis showed that this was true for groups A and B, although no significant change in the mean tHcy concentration occurred in group C during placebo treatment (**Table 2**). The change in tHcy was not significantly different in subjects reporting regular intake of B vitamins from that in those not regularly taking supplements before the washout phase. Despite these fluctuations, tHcy concentrations at the start of the vitamin treatment period did not differ significantly among groups.

After vitamin treatment for 4 wk, the mean tHcy concentration was reduced significantly in all groups ($P < 0.001$). The decrease in tHcy varied according to the treatment regimen: the most pronounced tHcy reduction was observed in group C (−18% compared with the tHcy concentration at week 4, corresponding to a geometric mean ratio of 0.82; Table 2). In group B, the tHcy concentration at week 8 was 15% lower than that at week 4. When folic acid was given alone (group A), the reduction in the plasma tHcy concentration was 11%. The difference in tHcy-lowering effect between group A and group C was significant ($P < 0.05$, ANOVA with Scheffe post hoc test).

The individual changes in tHcy concentration after 4 wk of vitamin treatment are shown in **Figure 1**. The change in tHcy was dependent on the tHcy concentration before vitamin supplementation (week 4); subjects with a high initial tHcy concentration responded to treatment with larger reductions in tHcy than those in subjects with initially low tHcy concentrations. Above a tHcy concentration of 8 μmol/L, each subject responded to vitamin supplementation with a decrease in tHcy after 4 wk. The extent of tHcy reduction was more pronounced when only the subjects with a tHcy concentration >8 μmol/L before treatment were considered (group A:−16%; group B:−20%; group C:−22%), even though the additional effect of vitamin B-12 on tHcy reduction was smaller ($P = 0.08$, ANOVA). Below a tHcy concentration of 8 μmol/L, the extent of tHcy reduction in group C (−14%) was significantly larger than in group A (−5%) ($P < 0.05$, ANOVA with Scheffe post hoc test), whereas it was intermediate in group B (−10%).

The change in tHcy was also dependent, although to a lesser extent, on the plasma folate concentration before vitamin supplementation. The largest reductions in tHcy were observed in women with the lowest initial plasma folate concentrations (**Figure 2**). In every subject with a plasma folate concentration <20 nmol/L, tHcy concentrations decreased after vitamin treatment, whereas this was not always the case for women with higher plasma folate concentrations. However, when plasma folate at the onset of vitamin treatment was >20 nmol/L, subjects seemed to benefit from the addition of vitamin B-12 (tHcy reduction in group C:−17%, group B:−12%) compared with the administration of folic acid alone (tHcy reduction in group A:−10%) (A compared with C: $P < 0.05$, ANOVA with Scheffe post hoc test). In contrast, for women with a plasma folate concentration ≤20 nmol/L, the change in tHcy was slightly more pronounced but not significantly different across treatment groups.

When tHcy and plasma folate concentrations before vitamin treatment (week 4) were included in the ANOVA as covariates, in addition to the significant differences between groups C and A, the tHcy reduction observed in group B was significantly larger than that observed in group A ($P < 0.03$). Change in tHcy was not related to RBC folate or plasma vitamin B-12 concentrations before vitamin supplementation; inclusion of these variables as covariates in the ANOVA did not improve the model.

Folate

At week 0, participants had plasma folate concentrations in the normal range (all but one >9.9 nmol/L; all >6.8 nmol/L) (23, 24). As expected, during the placebo phase, no changes in plasma folate concentrations were observed (**Table 3**), indicating also that any effects due to vitamin supplementation before the study began could be neglected.

Because of the laborious procedure for measurement of RBC folate, this index was measured only at weeks 4 and 8 to investigate the relation with plasma folate and tHcy as well as the response to folic acid supplementation. A strong positive associ-

TABLE 2
Response of plasma total homocysteine (tHcy) concentrations to placebo (week 4) and supplementation with folic acid or folic acid plus vitamin B-12 (week 8)[1]

	Plasma tHcy			
	Week 0 (baseline)	Week 4	Week 8	Mean ratio, week 8/week 4[2]
Group A ($n = 51$)	7.88 ± 2.22 (7.58)	8.13 ± 2.14 (7.84)[3]	7.18 ± 1.62 (6.99)[4]	0.89
Group B ($n = 49$)	7.52 ± 1.78 (7.31)	8.18 ± 2.41 (7.87)[3]	6.81 ± 1.46 (6.65)[4]	0.85
Group C ($n = 50$)	8.18 ± 1.74 (8.01)	8.12 ± 1.92 (7.91)	6.59 ± 1.12 (6.50)[4]	0.82

[1] $\bar{x}$ ± SD; geometric mean in parentheses. Group A received 400 μg folic acid/d, group B received 400 μg folic acid + 6 μg vitamin B-12/d, and group C received 400 μg folic acid + 400 μg vitamin B-12/d.
[2] Geometric mean ratio of tHcy at week 8 divided by tHcy at week 4; values <1 indicate a decrease in tHcy after vitamin treatment.
[3] Geometric mean significantly different from week 0 (baseline), $P < 0.05$ (paired t test).
[4] Geometric mean significantly different from week 4, $P < 0.001$ (paired t test).

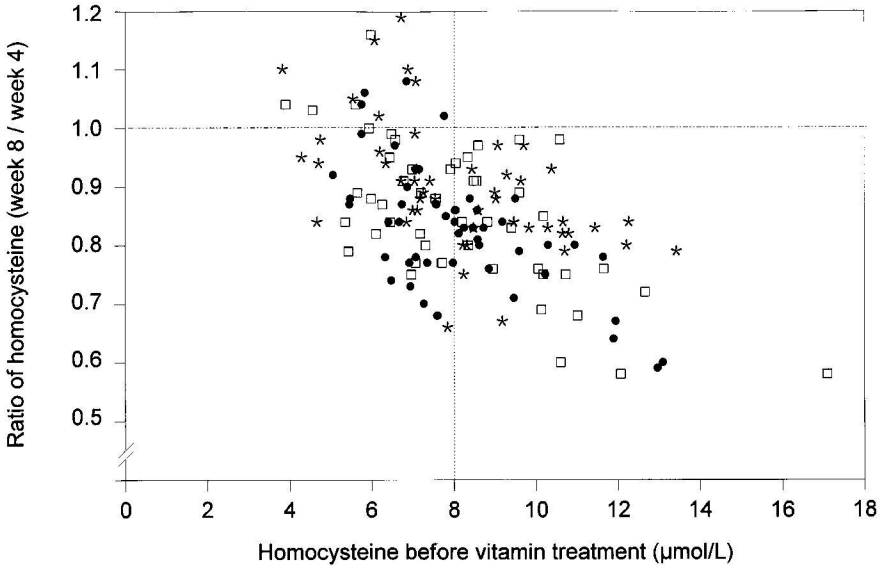

FIGURE 1. Change in the total homocysteine (tHcy) concentration in relation to the tHcy concentration before vitamin supplementation (week 4). The ratio was derived by dividing the concentration of tHcy at week 8 by the concentration at week 4. Values <1 indicate a decrease in tHcy after vitamin supplementation. *, supplementation with 400 µg folic acid/d; □ supplementation with 400 µg folic acid + 6 µg vitamin B-12/d; ● supplementation with 400 µg folic acid + 400 µg vitamin B-12/d.

ation was observed between plasma folate and RBC folate at week 4 ($r = 0.5436$, $P < 0.001$). Even though 3 of 150 subjects had low RBC folate concentrations at this time point (<317 nmol/L, or 140 ng/mL), their folate status seemed to be normal as indicated by their corresponding plasma folate and tHcy concentrations. Mean plasma folate and RBC folate concentrations at the start of the vitamin treatment did not differ among the 3 groups ($P > 0.05$, ANOVA). After 4 wk of vitamin supplementation, all treatment groups showed significant increases in mean plasma and RBC folate concentrations ($P < 0.001$ for both). The extent of the mean increase varied between 52% and 55% (plasma folate) and 69% and 78% (RBC folate) when compared with the values at week 4, and were not significantly different between the groups ($P > 0.05$, ANOVA) (Table 3).

Vitamin B-12

At week 0, the geometric mean plasma vitamin B-12 concentration for all groups combined was 268 pmol/L (Table 3). Five

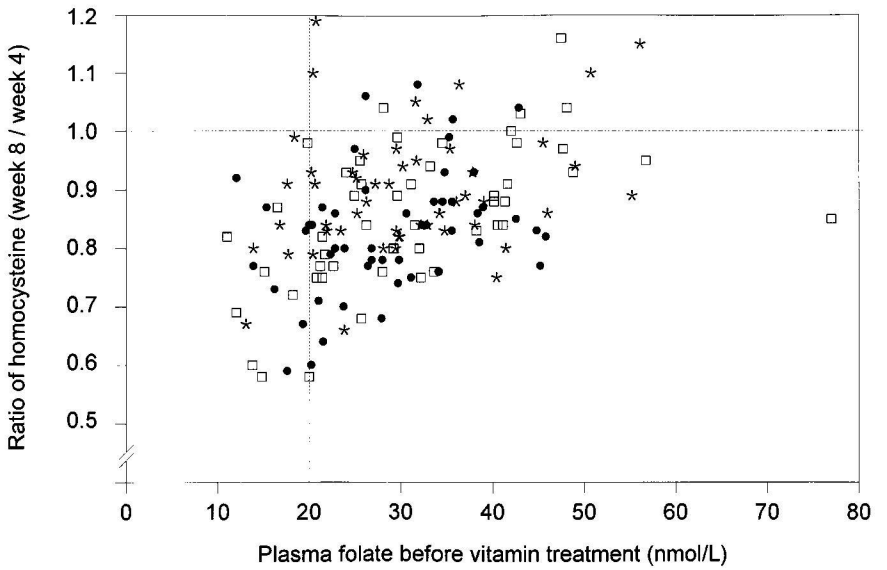

FIGURE 2. Change in the total homocysteine (tHcy) concentration in relation to the plasma folate concentration before vitamin supplementation (week 4). The ratio was derived by dividing the concentration of tHcy at week 8 by the concentration at week 4. Values <1 indicate a decrease in tHcy after vitamin supplementation. *, supplementation with 400 µg folic acid/d; □ supplementation with 400 µg folic acid + 6 µg vitamin B-12/d; ● supplementation with 400 µg folic acid + 400 µg vitamin B-12/d.

TABLE 3
Response of plasma vitamin indexes to placebo (week 4) and supplementation with folic acid or folic acid plus vitamin B-12 (week 8)[1]

	Week 0 (baseline)	Week 4	Week 8
Total group (n = 150)			
Folate (nmol/L)	29.8 ± 11.4 (27.6)	30.2 ± 10.7 (28.3)	45.6 ± 14.3 (43.5)[2]
RBC folate (nmol/L)	—	847 ± 381 (782)	1485 ± 615 (1359)[2]
Vitamin B-12 (pmol/L)	292 ± 119 (268)	276 ± 110 (253)[3]	345 ± 144 (317)[4]
PLP (nmol/L)	51.5 ± 25.0 (46.2)	—	—
Group A (n = 51)			
Folate (nmol/L)	30.1 ± 10.4 (28.2)	30.5 ± 10.2 (28.8)	46.6 ± 17.4 (43.8)[2]
RBC folate (nmol/L)	—	810 ± 295 (759)	1438 ± 643 (1296)[2]
Vitamin B-12 (pmol/L)	268 ± 100 (251)	251 ± 102 (233)[3]	259 ± 104 (240)
PLP (nmol/L)	53.9 ± 27.9 (47.8)	—	—
Group B (n = 49)			
Folate (nmol/L)	31.7 ± 13.4 (28.9)	31.3 ± 12.9 (28.8)	46.1 ± 13.4 (44.1)[2]
RBC folate (nmol/L)	—	896 ± 428 (812)	1551 ± 593 (1443)[2]
Vitamin B-12 (pmol/L)	329 ± 123 (307)	313 ± 111 (292)	371 ± 125 (353)[2]
PLP (nmol/L)	53.5 ± 26.0 (47.7)	—	—
Group C (n = 50)			
Folate (nmol/L)	27.6 ± 10.0 (25.9)	28.8 ± 8.6 (27.4)	44.0 ± 11.4 (42.5)[2]
RBC folate (nmol/L)	—	836 ± 412 (779)	1468 ± 616 (1344)[2]
Vitamin B-12 (pmol/L)	279 ± 125 (250)	265 ± 109 (239)	407 ± 158 (377)[2]
PLP (nmol/L)	47.0 ± 20.4 (43.4)	—	—

[1] $\bar{x}$ ± SD; geometric mean in parentheses. Group A received 400 μg folic acid/d, group B received 400 μg folic acid + 6 μg vitamin B-12/d, and group C received 400 μg folic acid + 400 μg vitamin B-12/d. RBC, red blood cell; PLP, pyridoxal-*P*.
[2] Geometric mean significantly different from week 4, $P < 0.001$ (paired t test).
[3] Geometric mean significantly different from week 0 (baseline), $P < 0.01$ (paired t test).
[4] No statistical test performed because of the difference in vitamin B-12 treatment among the 3 groups.

participants had plasma concentrations indicative of a suboptimal vitamin B-12 status (<111 pmol/L, or <150 pg/mL) (25). Their corresponding plasma tHcy concentrations ranged from 7.3 to 12.0 μmol/L.

After 4 wk of placebo treatment, the geometric mean vitamin B-12 concentration of the whole group was slightly but significantly lower than at week 0 ($P < 0.01$). This was mainly attributable to changes in group A ($P < 0.01$). The observed change did not correlate with the change in tHcy concentration during the placebo period ($P = 0.2$). At week 4, the plasma vitamin B-12 concentration of group A was significantly lower than that of group B ($P < 0.05$, ANOVA with Scheffe post hoc test).

From week 4 to week 8, no further changes in vitamin B-12 concentrations occurred in the group receiving folic acid only. In group B, the vitamin B-12 concentration increased significantly by a mean value of 58 pmol/L ($P < 0.001$). In group C, the plasma vitamin B-12 concentration increased by a mean value of 142 pmol/L ($P < 0.001$). This increase was significantly higher than that in group B or group A ($P < 0.05$, ANOVA with Scheffe post hoc test).

Vitamin B-6

Because vitamin B-6 was not a target index in this study, plasma PLP concentrations were measured only at the beginning of the study. PLP concentrations ranged between 16.4 and 168.9 nmol/L, with a geometric mean across all groups of 46.2 nmol/L.

DISCUSSION

The role of folic acid in the prevention of NTDs and vascular diseases and the potential additional effect of vitamin B-12 is a matter of debate. In this study, we investigated whether a combination of these vitamins had a more pronounced tHcy-lowering effect than supplementation with folic acid alone. Of the young women participating in this study, the vast majority had an adequate status of the vitamins involved in homocysteine metabolism, according to currently accepted guidelines, and they were normohomocysteinemic as defined by Kang et al (26). Despite this, folic acid supplementation (alone or in combination with vitamin B-12) resulted in significant reductions in plasma tHcy concentrations.

Ward et al (6) administered folic acid in amounts that could be reached through optimal food selection or use of fortified foods (100, 200, and 400 μg folic acid/d) to lower tHcy concentrations in middle-aged, healthy men. Because in their study the supplementation regimen was increased over the course of the study in 6-wk intervals, no information on the tHcy-lowering effect attributable solely to supplementation with 400 μg folic acid can be obtained. However, as in our study, the tHcy-reducing effect was clearly dependent on the tHcy concentration at baseline. Before supplementation, men in the 2 lowest tertiles together had a mean plasma tHcy concentration of 8.09 μmol/L, which is almost identical to that observed in group A in our study. After folic acid administration, the extent of tHcy reduction in group A was comparable with the reduction observed by Ward et al (6) in the 2 lowest tertiles over a much longer supplementation period.

Boushey et al (4) and Tucker et al (27) estimated that an increase in folic acid intake of ≈200 μg/d results on average in a reduction in tHcy concentration of 4 μmol/L, or 12%. However, this rather high effect of folic acid supplementation may be restricted to subjects with moderate or intermediate hyperhomocysteinemia, as observed previously (10, 28). Our findings and results from others (6) indicate that in normohomocysteinemic subjects, twice the amount of additional folic acid, ie, 400 μg/d is required for a mean reduction of the plasma tHcy concentration of 11%. Even though we are still awaiting results from interven-

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