The Chilean Flour Folic Acid Fortification Program Reduces Serum Homocysteine Levels and Masks Vitamin B-12 Deficiency in Elderly People

ABSTRACT Hyperhomocysteinemia is considered a risk factor for cardiovascular disease and is prevalent in the elderly. Supplementation with folic acid, vitamin B-6 and B-12 lowers homocysteine levels. In January 2000, the Chilean government initiated a flour folic acid fortification program to decrease the occurrence of neural tube defects. The aim of this study was to evaluate the effect of this program on serum homocysteine and folate levels in elderly subjects after 6 mo. A total of 108 elderly people were studied. We measured serum folate, homocysteine and vitamin B-12 levels before the fortification started and 6 mo later. At baseline, folate deficiency (<6.8 nmol/L) was present in 1.8%, vitamin B-12 deficiency (<14 pmol/L) in 31% of the sample. Six months later, serum folate levels increased from 16.2 ± 6.2 to 32.7 ± 7.1 nmol/L (P < 0.001), homocysteine levels decreased from 12.95 ± 3.7 to 11.43 ± 3.6 μmol/L (P < 0.001) and vitamin B-12 levels were unchanged. Flour fortification with folic acid had a moderate lowering effect on homocysteine levels. Given that vitamin B-12 deficiency was more common than folate deficiency, it may be more appropriate to add vitamin B-12 to food, at least in foods for this age group. J. Nutr. 132: 289–291, 2002.

KEY WORDS: • folic acid fortification • homocysteine
• elderly people • vitamin B-12

Hyperhomocysteinemia is considered to be an independent risk factor for cardiovascular disease (1). Plasma levels are determined by genetic and nutritional factors. Folic acid, vitamin B-6 and B-12 levels are inversely related to homocysteine levels (2). Several trials have demonstrated the lowering effect of folic acid, vitamin B-6 and B-12 supplements on homocysteine levels (2). From a public health perspective, this is a very interesting issue because hyperhomocysteinemia in elderly people is highly prevalent (3,4). Therefore, fortified foods could prevent hyperhomocysteinemia and, in the long term, cardiovascular disease.

In the past decade, some trials showed that folic acid intake before conception reduced a woman’s risk of bearing a child with a neural tube defect (5). For these reasons, in January 2000, the Chilean government initiated a program of folic acid fortification, with 320 μg of synthetic folic acid/100 g of wheat flour. It is important to evaluate the effect of the national folic acid fortification program on serum homocysteine and folate levels in the elderly.

SUBJECTS AND METHODS

A prospective study was performed in Santiago for 6 mo, from December 1999 to July 2000. Free-living subjects (n = 149) assigned to three public outpatients clinics near their residences, aged ≥70 y and with low income, were invited by telephone to participate. Exclusion criteria were as follows: vitamin supplementation, wasting chronic illness or severe cognitive impairment, defined as a score of < 20 on the Mini Mental State Examination (6). This is the most widely used test to detect dementia and a score of < 20, out of a maximum of 30, is indicative of impairment. This score has also been validated in the Chilean elderly population (7).

All individuals signed a written informed consent before entering the study, which was approved by the Institutional Review Board of the Institute of Nutrition and Food Technology of the University of Chile. Of these, 19 refused to participate, 4 subjects died and 18 subjects were lost to follow-up. Thus, the final sample studied at baseline and at 6 mo was 108 subjects (67 women), aged 74.3 ± 3.7 y.

Clinical examinations were conducted and blood samples were obtained in December 1999, before the fortification of flour with folic acid started; these procedures were repeated in July 2000. After an overnight fast, 20 mL of venous blood was drawn for routine blood chemistry assessment (packed red cell volume, creatinine, glucose, total cholesterol, HDL cholesterol, triglycerides), homocysteine, folate and vitamin B-12 serum levels. Folate and vitamin B-12 were measured by an anion capture technique using Abbott kits (IMX system folate and B-12, Abbott Laboratories, Diagnostic Division, Abbott Park, IL). Serum homocysteine was also measured using an Abbott Kit (Abbott IMX homocysteine). This procedure is based on the fluorescence polarization immunoassay technology. Blood chemistry was measured using standard automated laboratory methods with Abbott commercial kits. Statistical analysis.

Statistical analysis was done using Statistica for Windows version 4.5 (StatSoft, Tulsa, OK). Results are expressed as means ± SD. Comparison of basal data between men and women was performed using t tests for variables with normal distribution and Kruskal-Wallis ANOVA median tests for those variables with a nonnormal distribution. To evaluate the changes after folic acid fortification, paired t test and Wilcoxon matched pairs tests were performed for variables with normal and nonnormal distribution, respectively. Pearson correlation coefficient was done to evaluate the relationship between serum homocysteine and folate and vitamin B-12 levels. Proportions were compared using χ² tests. Differences were considered significant at P < 0.05.
RESULTS

Serum HDL cholesterol was higher and vitamin B-12 levels tended to be higher (P = 0.06), whereas serum homocysteine and packed red cell volume were lower in women than in men (Table 1). Serum homocysteine levels were normally distributed, unlike folate and vitamin B-12 levels, which had a positive skewness, as shown in Figure 1. Folate deficiency (<6.8 nmol/L (8)) was observed in 1.8% and vitamin B-12 deficiency (<165 pmol/L (9)) was present in 27.6% of the sample. Thirty-one percent of the subjects had serum homocysteine levels >14 μmol/L (10). Homocysteine correlated negatively with folic acid (r = −0.33, P = 0.001) and vitamin B-12 levels (r = −0.22, P = 0.024).

After 6 mo of consuming foods made from flour fortified with folic acid, serum folate levels increased from 16.2 ± 6.2 to 32.7 ± 7.1 nmol/L (P < 0.001). Homocysteine levels decreased significantly by 11.7%, from 12.95 ± 3.7 to 11.43 ± 3.6 μmol/L (P < 0.001). The changes observed did not differ between sexes (men, 11.6% and women, 10.6%). Vitamin B-12 levels were unchanged (Fig. 1). The percentage of subjects with hyperhomocysteinemia decreased from 31 to 17% (P = 0.033). At 6 mo, homocysteine correlated better with vitamin B-12 levels (r = −0.45, P < 0.001) than with folic acid levels (r = −0.20, P = 0.003). The only significant hematologic change was a slight increase in mean corpuscular volume (from 89.6 ± 4.7 to 90.6 ± 4.4 fl, P = 0.001), but it remained within the normal range.

DISCUSSION

We found that increasing the amount of folic acid in the diet was associated with a moderate decrease in homocysteine levels in older persons, even if they had normal basal serum levels of folic acid. Based on the literature, a decline of only 11% in basal serum homocysteine levels was expected (11).

The wheat flour in Chile is fortified with 220 μg of synthetic folic acid/100 g of flour. Our elderly subjects consumed an average of 220 g of French bread per day, equivalent to 185 g of flour, containing 410 μg folic acid. Based on data obtained from abroad, The Ministry of Health estimated that this level of fortification would cover the target population

![Figure 1](https://academic.oup.com/jn/article-abstract/132/2/289/4687118)
(women of childbearing age) and would not adversely affect nontarget consumers of high amounts of flour, including elderly people or young men. Ward et al. (12) demonstrated that 400 μg of synthetic folic acid given daily reduced homocyst(e)ine concentrations. Nevertheless, in the Framingham Offspring Study cohort, those who took vitamin B supplements had lower plasma homocysteine than people who did not take these vitamins, even after the fortification of grain products with folic acid (13).

Higher doses of folic acid supplements (>1000 μg) could mask hematologic signs associated with vitamin B-12 deficiency. The diagnosis can be missed because irreversible neurological damage can occur even in the presence of normal hematology (14). In elderly people, dietary cobalamin absorption is reduced and clinical or subclinical deficiency is present in 15–30% (15).

In this study, we observed that flour fortified with folic acid is not appropriate for elderly people because vitamin B-12 deficiency is not corrected. Considering that one third of our subjects had a subclinical deficiency of this vitamin in the first evaluation, neurological and hematologic alterations could appear in the future. The slight increase in mean cell volume, even within the normal range, is probably an indicator of an ongoing cobalamin deficiency (14).

In conclusion, we demonstrated that flour fortification with folic acid in elderly people lowers homocysteine levels, but could also disguise vitamin B-12 deficiency. These results have important implications for food fortification policy.

LITERATURE CITED


