

Effect of Folic Acid Supplementation on Plasma Zinc Concentrations of Young Women

Timothy J. Green, PhD, C. Murray Skeaff, PhD, Susan J. Whiting, PhD, and
Rosalind S. Gibson, PhD

From the Department of Human Nutrition, University of Otago, Dunedin, New Zealand; and
the College of Pharmacy and Nutrition, University of Saskatchewan, Saskatoon,
Saskatchewan, Canada

OBJECTIVE: Women of reproductive age are advised to consume supplements or fortified foods containing at least 400 $\mu\text{g}/\text{d}$ folic acid for the prevention of neural tubes defects. Concerns exist about the adverse effects of folic acid on zinc status.

METHODS: Seventy-eight women (18 to 49 y) were assigned for 12-wk to receive either a placebo or a 400 $\mu\text{g}/\text{d}$ folic acid supplement.

RESULTS: At 12-wk mean (95% CI) red cell folate increased by 431 (350–511) nmol/L in the supplemented group relative to placebo ($P < 0.001$) but there was no change in plasma zinc in either group ($P = 0.213$).

CONCLUSIONS: Folic acid supplementation does not reduce plasma zinc concentrations in women of childbearing age. *Nutrition* 2003;19:522–523. ©Elsevier Inc. 2003

KEY WORDS: folic acid, zinc, plasma zinc, red cell folate, women, supplements

INTRODUCTION

Health authorities in several countries recommend that women of reproductive age obtain at least 400 $\mu\text{g}/\text{d}$ of folic acid, through supplements or fortified foods, for the prevention of neural tube defects.¹ However, uncertainty remains concerning antagonistic nutrient interactions resulting from such an intake of folic acid.² Early research indicated an inhibition of zinc absorption by folic acid in rats³ and humans.^{4,5} The mechanism proposed was mutual inhibition of intestinal absorption,³ with negative zinc balance seen in persons with marginal zinc intakes.⁴ Subsequent studies found no measurable effect of high folic acid intake on zinc status of animals⁵ or humans^{5–7} or on zinc absorption in humans.⁷ Nevertheless, the Standing Committee on Dietary Reference Intakes of the US Institute of Medicine² recently recommended further study of this issue, especially in women.

We recently conducted a 12-wk placebo-controlled trial to assess the impact of folic acid supplements on red cell folate concentrations in women of childbearing age. This trial also provided us with an opportunity to examine whether folic acid supplements decreased plasma zinc concentrations. The existence of such an adverse effect was of particular concern in view of the lower biochemical zinc nutriture noted recently among young New Zealand women compared with earlier studies, attributed in part to reductions in intake of red meat.⁸

MATERIALS AND METHODS

The Human Ethics Committee of the University of Otago approved the study. A protocol for the main trial has been reported

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Correspondence to: Timothy J. Green, PhD, Department of Human Nutrition, University of Otago, PO Box 56, Dunedin, New Zealand. E-mail: tim.green@stonebow.otago.ac.nz

elsewhere.⁹ Briefly, women (18 to 49 y) with red cell folate concentrations between 295 and 905 nmol/L determined at screening were eligible. Participants had no diagnosed chronic disease, were not pregnant or planning a pregnancy, nor were they users of supplements or regular consumers of folic acid–fortified foods. Eligible women were assigned to receive a placebo or a 400 $\mu\text{g}/\text{d}$ folic acid supplement. Participants completed a lifestyle questionnaire at the start and a 3-d, weighed diet record between weeks 6 and 12. Energy and nutrient content of the diets was calculated based on the New Zealand Food Composition Database. Fasting venipuncture blood samples were taken from seated subjects at

TABLE I.

SUBJECT CHARACTERISTICS AT BASELINE*		
	Placebo (n = 43)	400 $\mu\text{g}/\text{d}$ of folic acid (n = 35)
Baseline characteristic		
Age (y)	24.3 \pm 6.6	24.3 \pm 6.1
Weight (kg)	67.3 \pm 9.8	64.9 \pm 11.3
Height (cm)	167.9 \pm 6.2	164.2 \pm 6.5
%Oral contraceptive users	41.9	48.6
%Smokers	11.6	14.3
%Avoid red meat	7.0	28.6
Daily dietary intakes		
Energy (MJ)	7.76 \pm 2.05	7.44 \pm 1.94
Protein (g)	69.2 \pm 20.4	67.9 \pm 19.5
Folate (μg)	270 \pm 111	224 \pm 71
Zinc (mg)	9.2 \pm 2.9	9.5 \pm 3.5
Iron (mg)	10.6 \pm 3.5	11.0 \pm 4.4
Fiber (g)†	19.0 \pm 8.0	17.7 \pm 7.1

* Values are mean \pm standard deviation.

† Fiber as non-starch polysaccharide.

TABLE II.

CHANGES IN PLASMA ZINC AND RED BLOOD CELL FOLATE CONCENTRATIONS DURING THE INTERVENTION PERIOD				
	Baseline†	Week 12†	Adjusted difference*	P
Plasma zinc ($\mu\text{mol/L}$)				
Placebo group ($n = 43$)	13.2 \pm 1.4	13.5 \pm 1.6		
Folic acid group ($n = 35$)	13.0 \pm 1.7	13.8 \pm 2.1	0.6 (–0.5 to 1.8)‡	0.213
Red cell folate (nmol/L)				
Placebo group ($n = 43$)	667 \pm 180	683 \pm 173		
Folic acid group ($n = 35$)	650 \pm 216	1104 \pm 305	431 (350–511)§	<0.001

* Mean difference (95% confidence interval) between supplemented and placebo groups at week 12.

† Mean \pm standard deviation.

‡ Adjusted for baseline plasma zinc ($P < 0.001$) and use of oral contraceptive agent ($P = 0.045$).

§ Adjusted for baseline red cell folate ($P < 0.001$).

baseline and at 12 wk for zinc and folate determinations by using trace-element-free collection tubes. Blood samples were refrigerated immediately after collection, and the plasma was separated within 2 h by using trace-element-free techniques. Plasma samples were analyzed for zinc by using flame atomic absorption spectrometry with a bovine serum-certified reference material (National Institute of Standards and Technology, Gaithersburg, MD, USA). Red cell folate concentrations were determined with the microplate technique using chloramphenicol-resistant *Lactobacillus casei* as the test organism.

Plasma zinc and red cell folate concentrations were available for 43 and 35 subjects on the placebo and the folic acid treatments, respectively. Possible differences in baseline participant characteristics of the treatment and placebo groups were tested with one-way analysis of variance for continuous variables and χ^2 analyses for categorical variables. The differences in plasma zinc concentration at week 12 between the folic acid group and the placebo group were determined by regression analysis, controlling for oral contraceptive use and baseline plasma zinc concentration. Similarly, the differences in red cell folate between the folic acid group and placebo group were adjusted for baseline red cell folate concentrations.¹⁰ Data are presented as the mean difference between the folic acid and placebo groups at week 12, adjusted for baseline values. Statistical analyses were performed with SPSS 10 for Macintosh software (SPSS Inc, Chicago, IL, USA).

RESULTS AND DISCUSSION

The placebo and the folic acid groups were similar in every respect except for the number of subjects avoiding red meat (Table I). However, statistical analysis suggested that this dietary pattern did not affect the plasma zinc levels. In addition, the intake of nutrients, in particular those that could affect zinc status (iron, folate, dietary fiber, and zinc) did not differ between groups. Plasma zinc and red cell folate concentrations at baseline were similar in both groups (Table II). After 12 wk of ingesting 400 $\mu\text{g/d}$ of folic acid or a placebo, there was no change in plasma zinc concentrations in either group ($P = 0.213$). Also, there was no significant interaction between oral contraceptive use and treatment with respect to plasma zinc. However, ingesting the folic acid supplement caused red cell folate to rise markedly, so that by week 12 the mean levels were 431 nmol/L higher ($P < 0.001$) than those of the placebo group after adjusting for baseline.

Results presented in Table II show that plasma zinc concentration at the end of the trial, although related to initial plasma zinc

concentrations ($P < 0.001$) and to use of an oral contraceptive agent ($P = 0.045$), were not affected by the folic acid supplementation. Hence, our data suggested that the ingestion of a 400 $\mu\text{g/d}$ folic acid supplement in women of childbearing age does not compromise zinc status. Our measurement of zinc status was fasting (pre-breakfast) plasma zinc, which according to the Standing Committee on Dietary Reference Intakes for zinc,² is the preferred index. Measured folic acid changes in plasma and red cell are reported in detail elsewhere.⁹

In summary, our study is one of several that did not find a significant effect of folic acid intake on plasma zinc concentrations. Many of these studies, however, included men^{5,11} or measured the effect of acute folic acid supplementation.^{5,7} Our results in young women confirm that folic acid supplementation does not reduce plasma zinc concentrations in women of childbearing age.

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