

## Folic acid fortification: is masking of vitamin B-12 deficiency what we should really worry about?<sup>1,2</sup>

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Mandatory fortification of flour with folic acid has reduced the number of neural tube defects in North America (1). The study by Wyckoff and Ganji (2) in this issue of the Journal suggests that fortification with folic acid may have led to correction of macrocytosis [ie, increased mean corpuscular volume (MCV) of red blood cells] caused by vitamin B-12 insufficiency. They wisely concluded that MCV should not be used as a marker for vitamin B-12 insufficiency.

In this retrospective cross-sectional study, the authors used laboratory results from individuals aged  $\geq 19$  y who had their serum vitamin B-12 concentrations and MCV measured in an academic hospital between 1 January 1995 and 31 December 2004. Folic acid fortification began on 1 January 1998. Only subjects with low serum vitamin B-12 concentrations (ie,  $< 258$  pmol/L) were included in the study ( $n = 633$ ). The proportion of these subjects without macrocytosis (ie, with normal MCV) was higher in the postfortification period ( $\approx 87\%$ ) and perfortification period ( $\approx 85\%$ ) than in the prefortification period ( $\approx 70\%$ ). However, the prefortification reference group consisted of only 86 subjects, which may mean that the prefortification estimate was less reliable than the other 2 estimates. Furthermore, they studied a group of patients from an academic hospital, which may make it difficult to generalize the results to the general population.

Two other studies have performed similar analyses. In contrast with the findings of Wyckoff and Ganji (2), Mills et al (3) found no increase in the number of veterans with a combination of low vitamin B-12 concentrations and no macrocytosis after the introduction of folic acid fortification. However, a study by Ray et al (4) in Canadian women aged  $\geq 65$  y supports the findings of Wyckoff and Ganji. Ray et al did not measure MCV, but they did show an increase in the number of women with high concentrations of folate and low concentrations of vitamin B-12 in their blood. Although the number of women with a combination of high folate and low vitamin B-12 increased 7 times, the prevalence still remained quite low, 0.61% (4).

From case studies, we know that a delay in the diagnosis of vitamin B-12 deficiency could lead to irreversible neuropathy. But how great are the chances that a doctor would not recognize a vitamin B-12 deficiency because an individual with suspected anemia has a normal MCV? In practice, this is probably a minor problem because, by now, every physician should know that measuring MCV does not give any clue to whether the patient has a vitamin B-12 deficiency. All doctors should be educated to not just measure MCV to detect a vitamin B-12 deficiency, but rather

to measure concentrations of vitamin B-12 or methylmalonic acid in serum. It is fair to say, though, that the issue of which measurements and cutoff values should be used to determine a vitamin B-12 deficiency has not been settled (5, 6).

But what if the correction of macrocytosis is not only a doctor's problem, but is also a patient's problem? It is possible that the correction of anemia by consuming extra folic acid intake may not only correct the macrocytosis but may also lead to less fatigue among patients. This may delay the time that it takes for a person to visit the general practitioner to the point that neurologic damage may already have occurred. However, as far as we know, there are no data available to substantiate whether this is a realistic scenario or not. Nevertheless, we should not exclude the possibility of such a delay in patients with vitamin B-12 deficiency who live in a country with folic acid fortification.

Is a delayed diagnosis of vitamin B-12 deficiency by folic acid really the only worry? In the January issue of the Journal (7), it is reported that a combination of high serum folate concentrations and low vitamin B-12 status was associated with a higher risk of cognitive impairment in US subjects aged  $\geq 60$  y. In contrast, high serum folate concentrations in combination with a normal vitamin B-12 status were associated with a lower risk of cognitive impairment. This finding suggests that treating, and preferably preventing, vitamin B-12 deficiency is crucial in the era of folic acid fortification. How can we prevent vitamin B-12 deficiency? One option might be to cofortify flour with folate and vitamin B-12. In a group of 189 healthy volunteers aged 50–85 y, Tucker et al (8) showed that consumption of 1 cup (0.24 L) of breakfast cereal fortified with 400  $\mu\text{g}$  folic acid, 2 mg vitamin B-6, and 6  $\mu\text{g}$  vitamin B-12 significantly increased mean ( $\pm$ SEM) vitamin B-12 concentrations in serum from  $296 \pm 10$  to  $354 \pm 13$  pmol/L after 12 wk. Furthermore, the percentage of subjects with vitamin B-12 concentrations  $< 185$  pmol/L decreased from 9% to 3%. Although this does not prove that cofortification will prevent all vitamin B-12 deficiencies, it is likely to improve the vitamin B-12 status in the general population and to prevent some of the alleged side effects of folic acid fortification.

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But will cofortification with folate and vitamin B-12 solve all the issues currently considered in the ongoing debates on whether or not to fortify food with folic acid in other countries? Probably not, because there are indications that high doses of folic acid may promote the growth of existing tumors (9) or may interfere with antifolate drug therapy (10).

In conclusion, it is uncertain to what extent the masking of vitamin B-12 deficiency by folic acid is indeed a worry. Doctor's delay appears to be a nonissue if appropriate markers of vitamin B-12 are measured, but patient's delay should be considered. Considering the ongoing discussion of what the best markers and cutoff values for vitamin B-12 deficiency are, it is also hard to say how many people would be at risk. Other possible negative effects of folic acid fortification should be further investigated and thoroughly evaluated. Cofortification with vitamin B-12 may solve some, but not all, of the possible adverse effects.

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