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EDITORIAL

Folic acid fortification: the good, the bad, and the puzzle of vitamin B-12[1,2]

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> *Policy decision making in any country considering fortification with one or several micronutrients should not be limited to the documentation of the indications for fortification. ... A plan for evaluating the effectiveness and safety of the intervention is also needed* (1).

We would not be allowed to conduct a clinical trial of a drug without proper monitoring procedures for both expected and unexpected outcomes; however, such a scenario occurred in 1998 when the Food and Drug Administration mandated that flour products in the United States be fortified with folic acid (pteroylglutamic acid)—a substance forming only a very minor component of the folates in unfortified food (2). The argument then was that randomized clinical trials had proven that folic acid taken in very early pregnancy can markedly reduce the risk that an infant will be born with a neural tube defect (NTD). The consequence was, however, that for each NTD prevented, several hundred thousand people were to be exposed, without choice, to extra folic acid. Despite this concern, no studies have been carried out in nonchildbearing subsets of the population to see whether they might also benefit from, or could even be harmed by, exposure to folic acid. The prevailing view was that it must be "a good thing" to give extra folic acid, not only to prevent NTDs but also to lower plasma homocysteine concentrations and perhaps prevent cardiovascular disease. Although folic acid fortification has reduced the number of NTDs (3), recent trials suggest a limited effect, or no effect, of folic acid intervention on cardiovascular disease, although the outcome may not be entirely negative (4-6).

In the absence of formal federal monitoring of possible undesirable effects of fortification, the academic research community has been left to take up the challenge, and recent studies have resulted in increasing cause for concern. In this Journal, Kim (7) raised the question in 2004 of whether folic acid fortification would prevent or promote cancer, a question still not answered (8). In 2005, an increased risk of cognitive decline was reported in elderly persons who took folic acid supplements in doses >400 μg/d (9). However, an interaction between folate intake and vitamin B-12 intake was observed such that the cognitive decline was less marked in those who also took high-dose vitamin B-12–containing supplements.

Two other recent reports deserve special attention because they have shown that some sectors of the population might suffer adverse effects from folic acid fortification. In this issue of the Journal, Morris et al (10) report on a group of nearly 1500 healthy elderly persons aged ≥60 y in whom anemia, macrocytosis, and cognitive function were assessed. The test used for cognitive function, the Digit Symbol-Coding subtest of the Wechsler Adult Intelligence Scale III, is well validated and is quite sensitive to cognitive impairment; it mainly reflects processing speed but also tests memory. This subset of the US National Health and Nutrition Examination Survey cohort was studied between

1999 and 2002, well after the time when food began being fortified with folic acid. As expected, a substantial proportion (20%) of the cohort had a high concentration of serum folate, defined as a concentration >59 nmol/L. Interestingly, Morris et al report both a "good" and a "not-so-good" side of folate. In agreement with current knowledge, they found that a low vitamin B-12 status is associated with macrocytosis, anemia, and cognitive impairment. The key finding in this report concerns interactions between folate status and vitamin B-12 status. The "good news" is that, in subjects with a normal vitamin B-12 status, high serum folate (>59 nmol/L) was associated with protection from cognitive impairment. This finding is remarkable in a population with a much higher mean folate concentration (39 nmol/L) than that seen in countries where there is no mandatory folate fortification. A similar result was reported for Latinos living in California, where higher red blood cell folate concentrations after fortification were associated with protection from cognitive impairment and dementia (11). Simply put, if your vitamin B-12 status is good, folate supplementation is good for you!

The "not-so-good" news from the study by Morris et al is that the relation between high serum folate and cognitive impairment was reversed in subjects who had a low vitamin B-12 status. Those with a low vitamin B-12 status (serum cobalamin <148 pmol/L) and high serum folate (>59 nmol/L) had an odds ratio for cognitive impairment of 5 compared with those whose vitamin B-12 status and folate status were both normal. This group, which had a low vitamin B-12 status and a high serum folate concentration also had an odds ratio close to 5 for anemia. Thus, the simple interpretation is that the cognitive impairment and anemia usually associated with low vitamin B-12 status are made much worse by a high folate status. As discussed by the authors, there has long been controversy about whether the administration of folic acid makes the symptoms of vitamin B-12 deficiency worse. The new findings are consistent with those of earlier studies in subjects with vitamin B-12 deficiency, ie, that low doses (300–800 μg/d) of folic acid can mask hematologic signs and may aggravate neurologic symptoms (12-14) and that the severity of neurologic impairment increases with rising serum folate concentrations (15).

Another recent report, by Troen et al (16), studied an index of immune function—natural killer (NK) cell cytotoxicity—in postmenopausal women and also showed both "good" and "not-so-good" sides of folic acid. NK cells are an important part of the nonspecific immune response and can kill tumor cells and virally infected cells. In this study the authors found an inverse U-shaped relation between total folate intake and NK cytotoxicity. Women in the bottom tertile of dietary folate intake (<233 μg/d) who took daily supplements containing ≤400 μg folic acid displayed better immune function than did those who took no supplementary folic acid; however, women with a dietary folate intake ≥233 μg/d who took supplements providing >400 μg folate/d had impaired NK cytotoxicity. Although a relation between total plasma folates and NK cytotoxicity was evident, a highly significant inverse linear association between the amount of folic acid in plasma and NK cytotoxicity was observed, particularly in women aged >60 y. The only important sources of folic acid are from fortified foods and dietary supplements. These findings raise the hypothesis that excess folic acid from supplements or from fortified food can suppress NK function, which is vital for normal immune function. This hypothesis could, and therefore should, be tested. It would also be of interest to know whether an association between vitamin B-12 status and NK cytotoxicity exists. Is it possible that poor vitamin B-12 status influences the metabolism of folic acid or the function of NK cells after high intakes of folic acid?

A notable feature of the 3 recent studies that described an adverse effect of high folate status is that many participants (33–67%) in each of the studies reported the use of folate-containing supplements (9, 10, 16). Folic acid is used to fortify food and is contained in almost all folate-containing supplements. Hence, these subjects were being exposed to folic acid from supplements as well as from fortified food—a matter that has already raised concern (17). It is perhaps not surprising that Troen et al (16) detected unmetabolized folic acid in fasting plasma samples from 78% of the subjects in their study.

Assuming that the findings of these studies will be confirmed, challenging questions about future research and health policies that relate to the puzzling interactions between folate and vitamin B-12 will need to be answered. Some of these questions are as follows:

1.) Is the balance between folate and vitamin B-12 status equally as important as the absolute concentrations of these vitamins? The application of mathematical modeling may help to answer this question (18).
2.) By what mechanisms does a high folate status in persons with a low vitamin B-12 status cause anemia and cognitive impairment?
3.) Is unmetabolized folic acid the culprit? Data from a small number of subjects in the United States indicate that folic acid accounts for 16% of the plasma folate in persons whose total plasma folate concentration is >50 nmol/L (19). More data on the prevalence and concentrations of folic acid in the blood are needed, the factors that influence it, and the effects it has on folate one-carbon metabolism.

4.) Given the recent findings, would it be safer to use methylfolate instead of folic acid as a supplement?
5.) Is the imbalance between folate and vitamin B-12 associated with any other adverse effects, particularly in vulnerable sectors of the population (eg, pregnant and lactating women and infants)? A preliminary report from India suggests that such an imbalance (low vitamin B-12 and high folate status) in pregnant mothers may have adverse effects on the health of their children (20).
6.) Is the complex relation between folate and cancer (8, 17) possibly a reflection in part of folate's interaction with vitamin B-12?

What are the wider implications of the new reports? The immediate concern relates predominantly to older persons. Morris et al found that ≈4% of the elderly persons they studied had a combination of low vitamin B-12 status and high folate status. If the same proportion of all elderly persons in the United States is affected, then ≈1.8 million elderly might be at increased risk of cognitive impairment and anemia because of an imbalance between folate and vitamin B-12. Thus, this large number of elderly at increased risk of cognitive impairment and anemia has to be balanced against the number of infants in whom NTDs are being prevented. Simply put, is it ethical to save one infant from developing an NTD and hopefully provide that child a high-quality life but increase the risk of poorer health in >1000 elderly persons? Questions that surely need to be discussed include the following:

1.) Should those calling for the addition of extra folic acid to food in the United States to further to reduce the number of infants with NTDs be required to show beyond reasonable doubt that such a step will not cause harm to others?
2.) Should the issue of fortifying food with vitamin B-12 be reopened in those countries that have already fortified certain foods with folic acid? An expert group has already recommended vitamin B-12 fortification in the Americas (21).
3.) Should countries considering folic acid fortification defer a decision until more is known about the interaction between folate and vitamin B-12 status? This question is particularly pertinent for the many countries that have a high prevalence of poor vitamin B-12 status (22, 23).
4.) Are sectors of the population, eg, vegetarians (24), pregnant and lactating women, infants, and ethnic groups with a poor vitamin B-12 status, being harmed by the existing level of folic acid fortification and supplement use?
5.) Is it of concern that, after folic acid fortification, children aged ≤5 y have the highest mean serum folate concentrations in the US population? Many (43%) of these children have concentrations >45 nmol/L (25).
6.) Should countries in South Asia, which have a high prevalence of NTDs (26), reconsider the need for folic acid fortification (27), especially in view of their high prevalence of vitamin B-12 deficiency (28), which itself might be one of the causes of NTDs (29)?
7.) Should supplements containing folic acid be combined with high doses of vitamin B-12 to ensure an optimal balance of the 2 vitamins?

It is time for a serious appraisal of how we move forward to continue to reap the benefits of folic acid for some members of our community without causing harm to others.

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