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## Folic Acid—Benefits, Risks, and Food Fortification

My last column addressed folic acid and its benefits for pregnant women and their offspring. Specifically, the column focused on: a) folate for women at childbearing age and folate's role in preventing both neural tube defects and other fetal abnormalities and learning and behavior problems in the offspring, and b) the possible benefits of folic acid for cancer prevention. This article continues the discussion of folate by addressing its effect on cognition and mental functioning and heart disease. Finally, the article will address the pros and cons of fortification.

### Folic Acid, Cognition, and Mental Health

B vitamins, including folic acid, have long been recognized as important for cognitive functioning and mental equilibrium. In a recent study, this was reaffirmed. Folic acid, as part of a vitamin-nutraceutical formulation (NF), containing vitamin B-12, vitamin E, S-adenosylmethionine, N-acetyl cysteine, and acetyl-L-carnitine, improved cognitive performance in both patients with Alzheimer's disease (2) (AD) and older subjects with no known cognitive impairment (3). After two weeks, three months, and six months of supplementation, respectively, those in this free-living trial receiving NF supplements, compared with those in the placebo group, performed significantly better on two batteries of normed tests on cognitive performance. However, for those participants over 74 years of age, NF supplementation was less effective. The study's authors suggested that this could be due to a) age-related malabsorption, b) other attendant nutritional deficiencies, c) age-related cognitive decline during the course of this study, or d) some combination of these. The overall findings of this study suggest a benefit of nutritional supplements containing folate as one of the ingredients for improved cognitive performance.

Data such as those seen with NF are corroborated by other findings in animal and human studies. One such finding using mice was reported in the *Journal of Alzheimer's Disease* (4). Folic acid was administered with the neuroprotective drug memantine, which is used in the treatment of moderate to severe AD. (It is an N-methyl-D-aspartic acid [NMDA] antagonist.) This is thought to help because the NMDA receptor—a glutamate receptor—is the predominant molecular device for controlling synaptic plasticity and memory function. In mice, folic acid worked synergistically with memantine to protect neurons from amyloid-beta accumulation. The protection was seen in cognitive tests. The folic acid-memantine treated group swam the Morris water maze in a shorter time than the other groups.

Human studies also note the relationship between folate and cognitive functioning. In Polish men and women, those with mild cognitive impairment, compared with matched controls (15), were more likely to have both elevated serum levels of homocysteine and very low levels of folate. These decrements were attendant with other vascular risk factors such as high blood pressure and the APOE4 allele, an allele associated with heart disease and brain amyloid-beta. However, in this small sample, there was no statistical difference in the progression toward dementia in the two groups. In contrast, in another study of 191 AD patients, there was an inverse relationship between cognitive performance and plasma levels of LDL, homocysteine, folate, and vitamin B-12 (6). However, the association between folate and the scores for performance on the Mini-Mental State Exam failed to remain significant after adjustment for age, sex, and status of statin treatment. Only plasma LDL cholesterol was significant after these adjustments. Nonconclusive data such as these led the authors of a recent review to suggest that, while the evidence for the efficacy of folate is improving cognitive symptoms, it is not clear-cut. They noted that part of the confusion in the data may be due to differences in folate form (11).

Factors associated with the subject such as gender can also have an impact. For example, Parkinson's disease (PD) patients (8) showed an inverse correlation between homocysteine levels and vitamin B-12 and folic acid in men, but found no such correlation in women. Further, this study showed that homocysteine levels were significantly higher in patients with cognitive impairment (nine out of 45 patients).

B vitamins, including folate, have not only been associated with cognitive functioning, they have also long been associated with mental health. Even mild folic acid deficiency is characterized by a string of symptoms associated with mental instability. More recently, folic acid supplementation has been shown to help reduce depressive symptoms (11,12). Some studies report that low folate and vitamin B-12, as well as overall low scores in measures like the healthy eating index, are associated with an increased risk of depression in older people (11). Some studies show that supplementation with folate and other micronutrients may help improve depressive symptoms in older patients. In addition, folate supplementation has been shown to work synergistically with commonly used antidepressants (18).

Despite some encouraging studies on the use of folate for improved cognitive functioning and greater mental stability, not all studies show a benefit of folate. Perhaps one reason is that the various folate forms used for supplementation—folic acid, 5-methyltetrahydrofolate (5-MTHF, also known as methylfolate and L-methylfolate), and folinic acid—have different bioavailabilities. This is made more complicated because of differences in utilization by patients with various genetic polymorphisms for folate and by those using alcohol and certain medications. For

example, folic acid supplementation of depressed patients with normal and low folate levels significantly reduced symptoms. Folate given with selective serotonin reuptake inhibitors appeared to be helpful in some depressed patients (11). The authors of the latter review mentioned concerns about too much folate masking B-12 deficiency, and even potentially worsening depressive symptoms. However, they also mentioned that folate is generally well tolerated and that use of the 5-MTHF form may reduce the likelihood of incurring some of these risks.

### **Folate, Coronary Disease, and Its Markers**

Epidemiological studies have linked increased blood levels of the amino acid homocysteine to an increased risk of cardiovascular disease (CVD). Thus, low serum folate and elevated serum homocysteine levels have emerged as risk factors for coronary heart disease. However, the relationship between folate and homocysteine is complicated, partially because of the many forms of folic acid, the interaction with B-12 in the so-called “folate trap,” and genetic differences in the alleles for enzymes controlling folic acid conversion to its various active forms. Three recent, comprehensive literature reviews all question the validity of adding folate and other B vitamins to the regimen for CVD patients (7,9,13). For example, the meta-analysis of randomized clinical trials involving 39,107 patients with preexisting coronary disease showed that interventions designed to lower homocysteine, including supplementation of folate, failed to change the risk of CVD.

Despite these reviews, smaller studies still suggest a potential relationship leaving much controversy about the role of low folate and elevated homocysteine in CVD. For example, in a study of 71 Japanese male smokers, the relationship between plasma homocysteine and folate levels was not significant. Homocysteine levels in the smokers were predictable by levels of the folate enzyme genotype coding for methylenetetrahydrofolate reductase (MTHFR). While the study elucidated complexities for the relationship between folate and homocysteine, it also showed that low plasma folate levels were related to other risk factors for CVD, specifically low HDL levels and impaired endothelial function. Thus, low folate levels may put smokers at risk for CVD irrespective of homocysteine levels. It may be important for smokers with low folate status to seek dietary and supplementary sources of folic acid (5).

Animal data add an interesting piece of information for consideration. Folate supplements administered to experimental animals at doses comparable to those given to humans appear to reverse endothelial dysfunction associated with diabetes (14). Since it is well known that diabetes greatly increases risk of CVD, more research is needed to understand the links between folate and CVD in insulin resistance and diabetes.

### **Folate Fortification—Questions Remain**

Blood folate levels, according to data from the National Health and Nutrition Examination Surveys (NHANES), of the U.S. population have improved after folate fortification. Both red blood cell folate, which measures long-term folate intake, and serum folate, which reflects recent folate intake, have increased. This is good because when red blood cell folate is low, there are attendant adverse health effects. Also, when serum folate is at low levels, this is an early indicator of inadequate folate status.

The elevation in both folate measures is associated with dramatic reductions in neural tube defects (NTDs) and other birth defects in North America and other countries adopting folate fortification. These measures have reduced the serious, costly, and heart-wrenching impacts of these preventable birth defects.

Similar gains have not been realized in countries that have adopted the strategy of directly supplementing women of child-bearing age. This strategy has two major failings. First, in order for folate supplementation to prevent NTDs, the folate status of the mother must be adequate when she conceives. In actuality, most women do not take supplements until after they realize that they are pregnant, which means that folate isn't present when it is needed to prevent these birth defects. Second, women of child-bearing age must obtain or purchase the supplement, and they must remember to take it.

An analysis of NHANES data just released in the Epub stage (17) affirmed that 24% of nonpregnant U.S. women of child-bearing age consumed the recommended usual intake of 400 µg. Cereals fortified with folic acid were the major foods contributing to the intake. Seventy-two percent of supplement users (containing folic acid) consumed the recommended usual intake. The numbers are gratifying in that one-fourth of the target population is reaching the goal, but also disconcerting because three-fourths are not.

The benefits of fortification during pregnancy and for the offspring are clear, while the benefits of fortification for the rest of the population remain controversial. Fortification programs must by their very nature benefit the at-risk group, hopefully benefit the entire population, and not put any part of the population at risk. In other words, programs must conform to an axiom of medicine, “At best, do no harm.” For the population overall, folate fortification offers some benefits. It appears to aid in the prevention of certain cancers for those whose folate status is low. Low levels of folate and high levels of serum homocysteine have been linked in epidemiological studies with CVD. Folate has been found helpful in the treatment of depression or in slowing cognitive decline, especially for those over 60. One study found that for seniors with adequate vitamin B-12, a higher serum 5-methyl tetrahydrofolic acid concentration was related to higher cognitive test scores (10). Another prospective study of more than 16,000 men showed that hearing loss over time was less in those with the highest total folate intake (16).

The benefits of folate fortification must be weighed against possible risks, including possible increased risk of some cancers, which has been alluded to with excess folate supplementation over long periods of time. However, the population segment for which the greatest concern exists is among the elderly with marginal B-12 status. In these individuals, the clinical consequences of vitamin B-12 deficiency may be worsened by high folic acid intakes. Further, symptoms indicating overt vitamin B-12 deficiency can be masked by folate supplementation.

Weighing the risks for one group with the benefits to others is never easy, especially since there are a number of forms of folate and the population carries a number of alleles of genes that metabolize folate. Better understanding of the bioavailability (1) and physiological effects of various folate forms, including free folate used for fortification, is needed. This is important because some think that the adverse effects of folate result from too much free folate.

Greater clarity is also needed regarding the effects of folate metabolites, as well as genetic differences in folate metabolism. Part of the confounding in literature may rest in the numerous gene alleles controlling the production of various folate metabolites. This potentially means that high levels of one moiety of folate may be helpful to persons carrying one allele and harmful to those carrying another. Added to the complexity is that folate from foods is adequately metabolized only if the conjugated form is deconjugated and if other water-soluble vitamins are present. Also, folate is metabolized differently in the presence of alcohol and certain drugs.

The recent 2010 analysis of NHANES data gave some assurances that the right level of folic acid was chosen for fortification (19). Specifically, only 2.7% of the population had daily intakes above the U.S. Institute of Medicine's upper level of 1,000 µg per day. The authors' conclusions, that it is unlikely that U.S. adults, who consume fortified food and supplements averaging up to 400 µg of folic acid per day, would exceed upper levels for folic acid, is comforting. Further, such data may help government agencies worldwide that are grappling with the issue as to whether to fortify. In terms of overall population benefits and the cereal chemist, the NHANES analysis showed that consumption of folate-fortified cereals and/or supplements was associated with higher serum folate and vitamin B-12 and lower homocysteine. These data for the U.S. population, where folate is listed by the 2005 Dietary Guidelines Advisory Committee as one of the "nutrients of concern," should provide evidence that folate fortification of grain-based foods is a beneficial strategy.

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