

Which supplement should we use: folic acid or methylfolate?

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Folic acid is an important nutrient that has multiple functions in the body. It plays a role in the synthesis of DNA and RNA, and is also involved in homocysteine and vitamin B₁₂ metabolism and in the functioning of the central nervous system and immune system. Folic acid supplementation has been shown to be effective for preventing neural tube defects and strokes. In some cases, it is also useful for the prevention or treatment of migraines, restless legs syndrome, osteoporosis, depression and other psychiatric disorders, psoriasis, gingivitis, cervical dysplasia, and certain other conditions. While folic acid itself is biologically inactive, it is converted *in vivo* to various biologically active folates, including 5-methyltetrahydrofolate (also called methylfolate or L-methylfolate) and 5,10-methylenetetrahydrofolate.

The nomenclature used to describe various folates is somewhat confusing. To a chemist, "folate" refers to the salt of folic acid. However, many nutritionists use the terms "folate" and "folates" to denote a spectrum of food-derived and biologically active endogenous compounds. In the discussion below, the nutritionist's terminology will be used, and folic acid will also be included as a folate compound.

Folate compounds that are commercially available include folic acid, methylfolate (also known as L-methylfolate, 5-MTHF, and 5-methyltetrahydrofolate), and folinic acid (5-formyl tetrahydrofolate). Folic acid is used most widely, because the vast majority of studies demonstrating clinical benefits of folates have used folic acid, and because it is chemically stable and relatively inexpensive. Folinic acid is used primarily in combination with certain anticancer drugs. Folinic acid is also an effective treatment for cerebral folate deficiency, a condition characterized by impaired transport of other folates across the blood-brain barrier. Methylfolate in relatively large doses (15 mg per day) has been found to be an effective adjunctive treatment for depression in patients who failed to respond to antidepressant medication alone.

Potential advantages of methylfolate

Recently, it has been argued that methylfolate is preferable to folic acid as a nutritional supplement. Some manufacturers have replaced folic acid with methylfolate in their multivitamin products, and some practitioners are of the opinion that products containing folic acid should not be used. One concern about folic acid is that it does not occur naturally in the body, and that people who take it have measurable concentrations of unmetabolized folic acid in their body. While unmetabolized folic acid has not been clearly shown to have deleterious effects, a few studies have linked folic acid supplementation to an increase risk of cancer, and the possibility that this effect is due to unmetabolized folic acid has not been ruled out. Another concern about folic acid is that some people, such as the 5-15% of the population that is homozygous for the 677C→T polymorphism of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene, might have difficulty converting folic acid to its biologically active form, and therefore might not benefit sufficiently from folic acid supplementation. In addition, methylfolate appears to be somewhat more bioavailable than folic acid, in that it raises plasma and erythrocyte folate levels to a greater extent than does folic acid.^{1 2} Furthermore, methylfolate is less likely than folic acid to mask the laboratory diagnosis of vitamin B₁₂ deficiency.³ It has also been argued that methylfolate is more effective than folic acid for lowering homocysteine levels. However, while one study showed a

small but statistically significant advantage of methylfolate over folic acid,⁴ 3 other studies found that the homocysteine-lowering effect of these compounds did not differ significantly.^{5 6 7}

Evidence is not sufficient to justify switching to methylfolate

After reviewing the available evidence, I have concluded that, despite some potential advantages of methylfolate, there is not sufficient evidence to justify routinely using it instead of folic acid. That conclusion is based on 2 main points. First, as mentioned above, the vast majority of the research demonstrating clinical benefits of folates has used folic acid. While a biologically active form of folate might theoretically be more effective than a precursor molecule, we do not know enough about how methylfolate as a supplement is transported and utilized in our cells and tissues to make assumptions about its comparative clinical efficacy. Randomized controlled trials are needed to determine whether methylfolate is more effective, equally effective, or less effective than folic acid for the prevention of neural tube defects and strokes, and for the prevention and treatment of other folate-responsive conditions.

Second, methylfolate is less stable than folic acid, a factor that could be particularly important when methylfolate is included in a multivitamin-multimineral preparation. Some compounds present in micronutrient formulations (such as vitamin C, copper, and thiamine) can react with and degrade other nutrients in the product, leading to a reduction in nutritional value and to the formation of potentially harmful degradation products. These types of reactions have been demonstrated to occur with vitamin B₁₂,⁸ whether they also occur with methylfolate has not apparently been investigated.

Folates and the MTHFR C677T polymorphism

With respect to the subset of the population that is homozygous for the MTHFR C677T genotype, the impairment of methylation of folic acid to its biologically active form is relative rather than absolute, and can apparently be overcome in most cases by supplementing with a modest dose of folic acid. For example, in one study, 41 patients with persistently elevated plasma homocysteine levels (approximately 75% of whom were homozygous for the MTHFR C677T polymorphism) were treated with 0.2 mg per day of folic acid. Plasma homocysteine levels fell in all but 2 cases within 7 weeks, and became normal within 7 months in 21 of 37 cases. Most of the remaining patients obtained normal homocysteine levels after taking 5 mg per day of folic acid for 7 weeks.⁹ In another study of patients with hyperhomocysteinemia who were treated with 5 mg per day of folic acid, the mean plasma homocysteine concentration fell by 40% among those who were homozygous for the MTHFR C677T genotype, but only by 23% among those with the CT genotype and by 10% in those with the CC genotype.¹⁰ In a study of people with elevated homocysteine levels and homozygosity for the MTHFR C677T genotype, 200 µg per day of folic acid tended to be more effective than 200 µg per day of methylfolate for lowering homocysteine levels.⁷ Taken together, these studies suggest that people who are homozygous for the MTHFR C677T genotype have a higher-than-normal folic acid requirement, but the studies do not support the claim made by some that folic acid supplementation is ineffective in people with the TT genotype or that methylfolate is a necessary or desirable alternative to folic acid in these individuals.

Folates and depression

It has also been claimed that methylfolate is the preferred form of folate to treat depression, but there is no published research to support that assertion. In one study, 15 mg per day of methylfolate as an adjunct to antidepressants was beneficial, whereas 7.5 mg per day was ineffective.¹¹ In contrast, a double-blind trial found that supplementation with 0.5 mg of folic acid per day increased the efficacy and reduced the side effects of fluoxetine in depressed women. The same dose of folic acid was ineffective in men, possibly because men have a higher dosage requirement, based on their greater body weight.¹² Another study found that 5 mg of folic acid per day was significantly more effective than 1.5 mg per day as an adjunct to antidepressant medication.¹³ Thus, daily doses of 0.5 mg and 5 mg of folic acid appeared to be beneficial, whereas a daily dose of 7.5 mg of methylfolate was not. These studies did not directly compare methylfolate and folic acid, and the patient populations may also not be comparable. However, the results are consistent with the possibility that folic acid is at least as potent as methylfolate in the treatment of depression. Moreover, in the study that used methylfolate, the presence of the MTHFR 677 CT/TT genotype was not significantly associated with a greater response to methylfolate.¹⁴ That observation does not support the claim made by some people that having one or two 677T alleles predicts the need for methylfolate.

Folates and cancer

With regard to folic acid and cancer, 2 randomized controlled trials found a significant increase in cancer incidence among people who received folic acid supplements.^{15 16} However, both of those trials were post hoc analyses of studies that were not designed to examine the relationship between folic acid and cancer. The results of post hoc analyses must be interpreted with caution, and researchers generally consider these types of studies to be "hypothesis generating" rather than proof of an effect. More recently, 3 different meta-analyses of 10 to 13 randomized controlled trials found that folic acid supplementation was associated with a non-statistically significant 5-7% increase in cancer incidence.^{17 18 19} Some investigators have suggested that in the short term, folic acid may accelerate the clinical expression of cancers that are already present, but in the long term it may prevent the development of cancer by enhancing immune function and by preventing DNA from mutating.²⁰ While questions regarding folic acid supplements and cancer remain unresolved, there is at present no clear evidence that methylfolate is safer than folic acid with regard to cancer risk.

Conclusion

Additional research is needed to determine how methylfolate compares with folic acid in terms of safety and efficacy. At present, routinely substituting folic acid with methylfolate, particularly in multiple-micronutrient products, is not supported by the available evidence.

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