
Folic acid vs. Methylfolate

Three misleading information to be clarified:

1. Supplemental Methylfolate* is natural.
2. People with mutation in MTHFR** cannot use folic acid due to methylation defect.
3. Supplemental methylfolate is a ready-to-work coenzyme form to be directly used as a methyl donor in the cell.

*Methylfolate: L-5-methyl-tetra-hydro-folate ($\text{CH}_3\text{-FH}_4$)

** MTHFR: methylene-tetra-hydro-folate-reductase

1. Supplemental Methylfolate is **NOT** natural.

- Folate from Foods is **NOT methylfolate**.
- Supplemental Methylfolate is **synthesized from folic acid (next slide)**.
- **Folic acid is twice more bioavailable than natural folate from foods**.

^a Dietary folate equivalents: 1 µg food folate = 0.6 µg of folic acid from fortified food or as a supplement consumed with food = 0.5 µg of a supplement taken on an empty stomach.

- **FDA recommends folic acid for grain fortification, **NOT methylfolate****

<http://www.nap.edu/catalog/6015/dietary-reference-intakes-for-thiamin-riboflavin-niacin-vitamin-b6-folate-vitamin-b12-pantothenic-acid-biotin-and-choline>

Supplemental Methylfolate is Synthetic

The pathway leading to the formation of methyl folate begins when folic acid (F), as folate, is reduced to dihydrofolate (DHF), which is then reduced to tetrahydrofolate (THF). The enzyme dihydrofolate reductase catalyses the last step. Vitamin B₃ in the form of NADPH is a necessary cofactor for both steps of the synthesis of DHF and THF.

Methylene-THF (CH₂THF) is formed from THF by the addition of methylene groups from one of three carbon donors: formaldehyde, serine, or glycine. Methyl folate (CH₃-THF) can be made from methylene-THF by reduction of the methylene group with NADPH. It is important to note that Vitamin B₁₂ is the only acceptor of methyl-THF. There is also only one acceptor for methyl-B₁₂ which is homocysteine in a reaction catalyzed by homocysteine methyltransferase. This is important because a defect in homocysteine methyltransferase or a deficiency of B₁₂ can lead to a methyl-trap of THF and a subsequent deficiency. Thus, a deficiency in B₁₂ can generate a large pool of methyl-THF that is unable to undergo reactions and will mimic folate deficiency. Another form of THF, formyl-THF or folinic acid, results from oxidation of methylene-THF or is formed from formate donating a formyl group to THF. Finally, histidine can donate a single carbon to THF to form methenyl-THF.

Compositions and methods for treating
depression
US 8372451 B2

Folic acid → DHF → THF → Methylene-THF → Methyl folate

Taking Vitamin B₁₂ along with folate is more important than worrying about folate form!

2. People with mutation in MTHFR can utilize folic acid and lower homocysteine

The T⁶⁷⁷ polymorphism in MTHFR results in a less stable enzyme but does not affect the affinity of substrates for the enzyme (R. M. Matthews, personal communication). Consequently, the metabolic effects of this polymorphism are lower amounts of enzyme activity rather than abnormal enzyme activity. In subjects with poor folate status, the homozygote would be expected to display lower MTHFR activity. However, for subjects with good folate status, the higher folate levels would stabilize the protein and reduce the difference in available enzyme compared with control subjects. It is expected that metabolic and adverse effects of this polymorphism would primarily affect people with poorer folate status. The level of folate

Currently, there is quite good evidence suggesting that the polymorphism has an adverse effect on homocysteine concentrations in subjects with relatively poor folate status (Selhub et al., 1993). However, there is no substantial evidence suggesting that this effect is not corrected by consuming the Recommended Dietary Allowance for folate that is presented in this report.

Mutated MTHFR is still functional but with marginally reduced activity, which can be corrected by higher intake of more bioavailable form of folic acid.

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No difference between folic acid and methylfolate in lowering homocysteine

TABLE 3 Erythrocyte and plasma folate concentrations in healthy men and women who consumed wheat rolls containing L-5-MTHF, folic acid, or placebo for 16 wk¹

Treatment	<i>n</i>	Baseline	wk 8	wk 16 ²	Difference at wk 16 ³
Intent-to-treat ⁴					
Erythrocyte folate, $\mu\text{mol/L}$					
L-5-MTHF	15	0.75 \pm 0.17	1.11 \pm 0.46	1.20 \pm 0.45 ^a	0.48 (0.27, 0.71)
Folic acid	15	0.79 \pm 0.18	1.16 \pm 0.30	1.14 \pm 0.38 ^a	0.37 (0.17, 0.57)
Placebo	15	0.84 \pm 0.21	0.91 \pm 0.23	0.85 \pm 0.27 ^b	
Plasma folate, <i>nmol/L</i>					
L-5-MTHF	15	38 \pm 11	56 \pm 22	56 \pm 22 ^a	23 (12, 34)
Folic acid	15	40 \pm 11	55 \pm 17	57 \pm 19 ^a	23 (12, 34)
Placebo	15	35 \pm 9	32 \pm 10	30 \pm 12 ^b	
As-treated ⁵					
Erythrocyte folate, $\mu\text{mol/L}$					
L-5-MTHF	13	0.78 \pm 0.16	1.20 \pm 4.34	1.30 \pm 0.40 ^a	0.54 (0.33, 0.77)
Folic acid	14	0.78 \pm 0.19	1.18 \pm 0.31	1.16 \pm 0.39 ^a	0.41 (0.19, 0.63)
Placebo	12	0.89 \pm 0.23	0.94 \pm 0.24	0.85 \pm 0.30 ^b	
Plasma folate, <i>nmol/L</i>					
L-5-MTHF	13	39 \pm 10	60 \pm 20	60 \pm 20 ^a	27 (14, 39)
Folic acid	14	40 \pm 12	56 \pm 17	59 \pm 19 ^a	26 (13, 39)
Placebo	12	36 \pm 9	33 \pm 10	31 \pm 13 ^b	

¹ Values are means \pm SDs unless otherwise stated. L-5-MTHF, calcium L-5-methyltetrahydrofolic acid.

² Baseline adjusted means \pm SDs. Means in a column without a common superscript letter differ, $P < 0.05$.

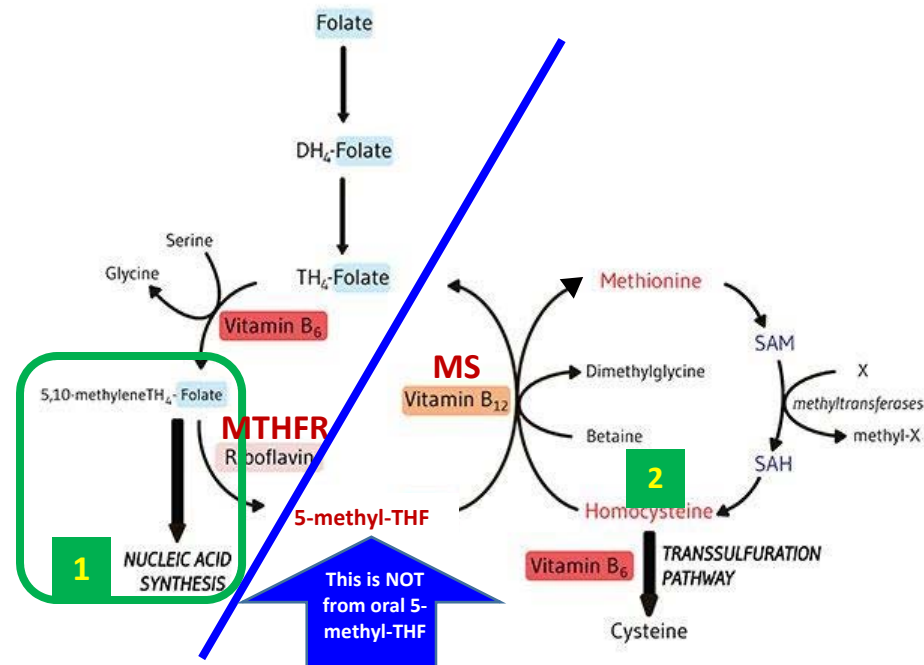
³ Values are means (95% CIs) adjusted for baseline concentrations relative to placebo.

⁴ Last value carried forward in the case of missing values.

⁵ Excludes dropouts.

3. Supplemental methylfolate is NOT the ready-to-use coenzyme form in the cell

Figure 2. Overview of One-Carbon Metabolism



5,10-methylenetetrahydrofolate is required for the synthesis of nucleic acids, and 5-methyltetrahydrofolate is required for the formation of methionine from homocysteine. Methionine, in the form of methyl donor S-adenosylmethionine (SAM), is essential to many biological methylation reactions, including DNA methylation. Methylenetetrahydrofolate reductase (MTHFR) is a riboflavin (FAD)-dependent enzyme that catalyzes the reduction of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate. SAM, S-adenosylmethionine; SAH, S-adenosylhomocysteine; TH₄-Folate, Tetrahydrofolate.

3. Supplemental methylfolate cannot be used directly in the cell because it has to be de-methylated before used in the cell.

The liver receives these two forms of folate and treats them in different ways. To the plain monoglutamate, it adds additional glutamates, thus converting it into the polyglutamate form for storage. As for the methyl form, the liver secretes most of it into bile and ships it to the gallbladder, whence it returns to the intestine again—an enterohepatic circulation route like that of bile itself (see Figure 5–17 on p. 121). Should the methyl folate be needed within the body, the methyl group would have to be removed—and the

Whitney, EN, Cataldo CB, Rolfes, SR. Understanding Normal & Clinical Nutrition, 3rd Ed. P 209, 1991

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Absorption, Transport, and Storage

Food folates (polyglutamate derivatives) are hydrolyzed to monoglutamate forms in the gut before absorption across the intestinal mucosa. This cleavage is accomplished by a γ -glutamylhydrolase, more commonly called folate conjugase. The monoglutamate form of folate is actively transported across the proximal small intestine by a saturable pH-dependent process. When pharmacological doses of the monoglutamate form of folate are consumed, it is also absorbed by a nonsaturable mechanism involving passive diffusion.

portal circulation. Much of this folate can be taken up by the liver, where it is metabolized to polyglutamate derivatives and retained or released into the blood or bile. Approximately two-thirds of the folate in plasma is pro-

Metabolism and Excretion

Before being stored in tissue or used as a coenzyme, folate monoglutamate is converted to the polyglutamate form by the enzyme folylpolyglutamate synthetase. When released from tissues into circulation, folate polygluta-

mates are reconverted to the monoglutamate form by γ -glutamylhydrolase. Folates must be reduced enzymatically and resynthesized to the polyglutamate form to function in single-carbon transfer reactions.

Institute of Medicine. Food and Nutrition Board (1998). Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington DC, National Academy Press..

3. Supplemental methylfolate is **NOT** the ready-to-use coenzyme form (Summary of Folate Metabolism)

1. Supplemental methylfolate can be absorbed and ends up in the liver via portal vein.
2. Liver will convert methylfolate to polyglutamate form of folate to keep it from escaping from the liver, but convert it back to methylfolate when releasing to the blood.
3. That is why methylfolate is the circulating form of folate, but it has to be converted to polyglutamate form to keep it until it functions in any cell (e.g., as a single-carbon donor).
4. If not converted to polyglutamate form of folate, the methylfolate will escape from the cell to the blood and circulate back to the liver.
5. Then, the liver will secrete most of methylfolate into the bile and ship it to the gallbladder.
6. The bile will be secreted to the intestine and the methylfolate will be reabsorbed when bile is reabsorbed via enterohepatic circulation.
7. Therefore, the methylfolate will be just recycling back without working in the cell if it is NOT de-methylated and polyglutamated in the cell.
8. **So, the methylfolate functioning in the cell is “re-methylated” from the folate in the cell:**
 - i. after the hydrolysis of “polyglutamate form of folate,” folate becomes tetra-hydro-folate
 - ii. tetra-hydro-folate becomes 5,10 methylene tetrahydrofolate (B6 needed as a cofactor)
 - iii. 5,10 methylene tetrahydrofolate becomes methyl-tetra-hydro-folate (Enzyme MTHFR and cofactor Vitamin B2 are needed for this reaction)

Summary on Folic Acid vs. Methylfolate

1. Supplemental Methylfolate is NOT natural.

2. Folic acid works for people with MTHFR Mutation.

- ✓ Studies show that **methylfolate** showed **NO advantage over folic acid**
- ✓ There is **NO recommendation by Authorities** that people with MTHFR mutation should take methylfolate.
- ✓ Most research used ***folic acid*** to prevent birth defects and to lower homocysteine level, **NOT methylfolate**.
- ✓ In Shaklee's Landmark Study, Nobody had elevated homocysteine level.
(among a group of 278 people taking Shaklee supplements containing folic acid for 20+ years)
 - ❑ Considering the fact that 10% of US population have homozygous MTHFR mutation, there should be about 27 people with elevated homocysteine if folic acid cannot lower the homocysteine.

3. Supplemental Methylfolate is NOT the ready-to-use coenzyme form.

4. More research is needed to recommend methylfolate for supplements to ensure the safety, especially, for women in childbearing age (folic acid vs. methylfolate vs. L-methylfolate : 43974 vs. 127 vs. 42 articles in PubMed)

Are you confident to tell your customers that Shaklee Vitamins containing folic acid work even with MTHFR mutation?

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