Research Review

Impairments in Folate Metabolism and the Benefits of L-5-MTHF

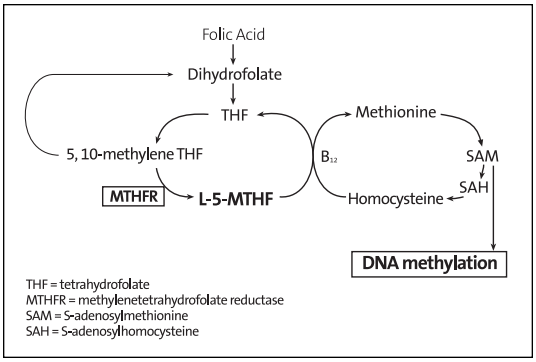
Scientific research has now clearly established a link between impairment in folate metabolism (i.e., the folate cycle) and risk to a variety of diseases. Impaired folate metabolism is most often clinically presented as high blood homocysteine (hyperhomocysteinemia). The list of diseases that have been strongly associated with an impairment in folate metabolism include: cardiovascular disease (CVD), stroke, colon cancer, depression, and Alzheimer's and Parkinson's diseases.[1-4] Hyperhomocysteinemia has been associated with low bone mineral density and fracture after menopause, insulin resistance syndrome (IRS), and dementia.[5-7] Furthermore, an impairment in folate metabolism has also been linked to altered estrogen metabolism, which may indicate a role in breast cancer.[8,9]

In many cases, the impairment in folate metabolism results from specific genetic alterations, or polymorphisms. When an alteration arises from a single nucleotide change in the DNA, it is called a single nucleotide polymorphism (SNP). A common SNP that can lead to impairment in folate metabolism is the C677T polymorphism of the methylenetetrahydrofolate reductase (MTHFR) gene. Approximately 7.2% of white women and 18.1% of Hispanic women in the United States are homozygous for the C677T MTHFR polymorphism; while 15%-20% of individuals are heterozygous for this polymorphism.[10]

While some polymorphisms have little effect on phenotype (the way genes are expressed), the SNPs in the MTHFR gene have been shown to result in a slower generation of L-5-methyltetrahydrofolate (L-5-MTHF) from 5,10-methylenetetrahydrofolate (Figure 1).

The formation of L-5-MTHF is the rate-limiting step in the metabolism of homocysteine and the generation of the active, usable methyl transfer substance S-adenosylmethionine (SAM). Lower levels of SAM are associated with increased levels of homocysteine.

Figure 1. **Folate metabolism.**



Recently, a meta-analysis of 40 published studies indicated that people with the MTHFR C677T polymorphism were at a significantly higher risk of coronary heart disease.[11]

It has been suggested that this risk may be overcome by supplementation with higher levels of folate and vitamins B_6 and B_{12} to support folate metabolism. For example, a study on folate intake and the MTHFR C677T polymorphism indicated that only the individuals with the polymorphism who had the *highest intake* of folate showed homocysteine levels similar to those individuals who did not have the polymorphism.[12]

In addition, research has indicated that a low blood level of folate, and possibly vitamin B_6, is associated with increased risk to breast cancer.[8,13] Because of this association and the new knowledge on polymorphisms that impair

folate metabolism, many researchers now suggest that women at higher risk to breast cancer, especially those with the MTHFR C677T polymorphism, may be in particular need of improved folate nutrition.[9,14]

It has also been shown that MTHFR polymorphisms increase the risk to low bone mineral density and fracture incidence after menopause.[5] The results of this study indicated that even when women were treated with hormone replacement therapy, the group of MTHFR TT (homozygote) genotypes had an increased fracture rate over other MTHFR genotypes. Interestingly, the MTHFR TT genotype was not related to differences in vitamin D, bone formation (i.e. osteocalcin), or bone loss (i.e. hydroxyproline) markers, but was associated with a 53% increase in plasma homocysteine. The authors state "...our results point toward an effect of MTHFR genotype on peak bone mass with early effects on fracture risk." Although no obvious difference was noted with the heterozygote genotypes, one could speculate that a subclinical alteration in bone structure may occur.

Folate is provided in several forms for commercial use including folic acid, 5-methyl tetrahydrofolate (5-MTHF), L-5-MTHF, and 5-formyl tetrahydrofolate (folacin). The 5-MTHF form of folate can be prepared synthetically, which leads to a racemic mixture of two isomers (or mirror image compounds): D-5-MTHF and L-5-MTHF. The active form of folate in the body is L-5-MTHF, which is also the predominant form of folate in the blood. L-5-MTHF is a particularly attractive supplement since it is unlikely to mask vitamin B_{12} deficiency. A major concern of high folate supplementation is that it can mask the hematological sign of vitamin B_{12} deficiency, which could delay diagnosis and provide opportunity for neurologic damage to occur.[15]

One of the initial studies investigating whether folacin supplementation could benefit individuals with the MTHFR C677T polymorphism is that of Stern et al.[16] In this study, the authors provided 5 mg doses of folacin to individuals homozygous for the MTHFR C677T polymorphism and to a control group of individuals not having this genetic impairment in folate metabolism. The study showed that both groups were capable of producing 5-MTHF* from the folacin. Unfortunately, this dose is far greater than most people would take and the risk of masking a vitamin B_{12} deficiency increases substantially at high levels of folacin supplementation, such as several mg per day.

It is known that the MTHFR C677T polymorphism does not block folate metabolism entirely, but makes it slow, or sluggish. The clinically relevant question then is: "Can an individual with the MTHFR C677T polymorphism produce enough L-5-MTHF from a reasonable intake of folate (less than 1 mg)?" Recent studies comparing 400 mcg per day of folic acid with an equal level of 5-MTHF in individuals with the MTHFR C677T polymorphism have found that both supplements show comparable efficacy in reducing homocysteine.[17,18] However, in these studies, the racemic form of 5-MTHF was used. That is, the synthetically prepared chemical mixture—providing only 50% as an active folate (L-5-MTHF) with 50% as the non-natural, mirror image structure (D-5-MTHF). Not only is the body incapable of using D-5-MTHF, but this non-natural form may compete with L-5-MTHF for uptake and activity. Therefore, these studies were actually comparing the effect of 200 mcg or less of active L-5-MTHF with 400 mcg folic acid, which suggests that L-5-MTHF was as effective at half the level. It is interesting to note that the individuals who took 5-MTHF also showed a prolonged beneficial effect resulting in statistically lower homocysteine levels that remained 6 months after supplementation was discontinued.[17] This prolonged beneficial effect was not seen in the individuals who had taken the folic acid supplement.

To evaluate the question of whether equal amounts of the nature-identical L-5-MTHF is comparable to equal amounts of folic acid, Venn et al. used 100 mcg levels of these two supplements in healthy women. In an initial study, the authors found that the low doses of L-5-MTHF and folic acid were able to increase blood folate levels to a similar extent in women of childbearing age.[19] In a subsequent placebo-controlled study, Venn et al. reported that the low dose of L-5-MTHF was more effective than folic acid in lowering homocysteine in healthy individuals.[15] Because individuals in these studies were not stratified for MTHFR polymorphisms, and given the prevalence of the MTHFR C677T polymorphism, one can propose

* When referring to the endogenous (in the body) form of folate, 5-MTHF is often used in the literature and refers to L-5-MTHF—the natural form of MTHF.

that the difference in effects between L-5-MTHF and folic acid would have been even greater in those who had impaired folate metabolism.

The effect of 5-MTHF (providing L-5-MTHF and D-5-MTHF) has also been evaluated for its ability to support endothelial function.[20] In this study, 5-MTHF was shown to interact with nitric oxide synthase, decreasing superoxide production while allowing for physiologically beneficial levels of nitric oxide to be produced, resulting in promotion of healthy endothelial cell function. This is a most interesting investigation since it suggests that 5-MTHF is capable of replacing tetrahydrobiopterin in beneficial support of endothelial cell function. This suggests that 5-MTHF may be a "normalizing" factor for endothelial function in those people with abnormal endothelial physiology.

Taken as a whole, these studies indicate that suboptimal folate metabolism is associated with increased risk to many diseases. These risks are amplified in people who have specific SNPs related to folate metabolism and are associated with increased blood levels of homocysteine. The bottleneck in folate metabolism that occurs as a consequence of the most common of these polymorphisms (i.e., the C677T MTHFR polymorphism) is in the conversion of 5,10-methylene-tetrahydrofolate to L-5-MTHF (Figure 1).

L-5-MTHF, as a supplement, may successfully bypass this bottleneck and, therefore, have a greater homocysteine-lowering effect than equal amounts of folic acid. It is for these reasons that L-5-MTHF may be preferred as a source of folic acid in nutritional therapy for homocysteine-related disorders. It is also important to point out that L-5-MTHF has a potential safety advantage over folic acid and folacin in that higher levels of L-5-MTHF will not block the hematological sign of vitamin B_{12} deficiency.

Key Points:

- Impaired folate metabolism and resulting hyperhomocysteinemia are associated with a number of conditions including cardiovascular disease, stroke, colon and breast cancers, bone fracture, insulin resistance syndrome, depression, and dementia.
- In many cases, impairments in folate metabolism result from specific genetic alterations or polymorphisms, such as the MTHFR C677T polymorphism.
- Approximately 40% of the population is affected by this polymorphism.
- High intakes (e.g., up to 5 mg) of folic acid and folacin are effective in reducing homocysteine, but this level of intake may be difficult to achieve and may also mask B_{12} deficiency.
- L-5-methyl tetrahydrofolate (L-5-MTHF) is a form of folate that: bypasses the MTHFR C677T polymorphism, is an effective alternative to high dose folic acid or folacin, and will not mask B_{12} deficiency.

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