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Lifestyle Longevity Program

MTHFR - Folic Acid, Homocysteine and Methionine
The Role of Genetic Mutations

MTHFR is a gene (called *methylene-tetra-hydro-folate reductase),* which controls the production of a specific reductase **enzyme** that converts *bio-inactive* folate (folic acid) into an active or *usable bioactive* form called *5-Methylfolate*. The MTHFR **enzyme** functions by adding a methyl group to the synthetic folic acid molecule; a conversion process called *methylation* and takes place within all the cells of the body. The body cannot manufacture folate; therefore, it needs to be ingested through diet and/or supplements. Folate is important in the production of red blood cells, proper growth and division of cells, and in preventing certain neural tube birth defects.

Folate:

The terms 'folate' and 'folic acid' are forms of vitamin B9 and are often used interchangeably, especially with supplements. The only difference between these two terms is that folate is a naturally occurring bioactive form of vitamin B9; whereas, folic acid refers to the synthetically manufactured form. Natural folate is found in dark green vegetables (e.g. broccoli, spinach) and dried legumes (e.g. chickpeas, beans, lentils) and yeast. The synthetic form is commercially manufactured and added to most *fortified* or enriched foods (e.g. cereals, milk products, flour, rice, oils) and is found in most vitamin supplements and prescriptions (e.g. Folgard). Normally, there is little nutritional difference between folate (natural) and folic acid (synthetic), as long as the synthetic form can be converted (metabolized) into its natural or bioactive form (*5-Methylfolate*) within the body's cells. Natural folate has the methyl group already attached and bypasses the enzymatic methylation step (See References).

When a genetic mutation of MTHFR is present there is a lack of normal amounts of this reductase enzyme, resulting in the body cells inability to convert inactive folic acid to bioactive *5-Methylfolate*. The can cause a functional metabolic 'folic acid deficiency', even though the blood level of 'folate' is normal. When this occurs there is a shift within the cellular pathway causing an increase in blood *homocysteine* levels.

Homocysteine:

Homocysteine is an amino acid that is part of the body's normal cellular methylation cycle. Its production within the cell is dependent on normal MTHFR enzyme function and adequate levels of *5-Methylfolate,* along with vitamin B12 and vitamin B6. Deficiencies in any of these may be associated with elevated homocysteine levels and certain types of anemia (e.g. Pernicious anemia).

A high level of homocysteine in the blood (called Hyperhomocysteinemia) makes the arteries in the body more prone to injury. This leads to inflammation in blood vessel walls, which in turn may lead to atherosclerosis (cholesterol plaque) formation and progression. Conditions that have been observed (but not necessarily proven) with MTHFR genetic mutations and elevated homocysteine levels include cardiovascular disorders (increased risk of peripheral artery disease, stroke, abdominal aortic aneurysm, hypertension, blood clots), increased risk of depression, autism, Alzheimer's disease and other forms of dementia or cognitive decline, osteoporosis, certain cancers, and pregnancy-related (neural tube defects) disorders.

Individuals with high homocysteine levels typically respond well to supplementation with folate (methylfolate), vitamin B6 (riboflavin) and vitamin B12 (methylcobalamin). It is also important to note that there are many persons with MTHFR mutations who do not have an elevated homocysteine level. Keep in mind that some patients have developed compensatory ways to counter the MTHFR mutation and may have sufficient active folate.

Methionine:

Another amino acid that is essential in the metabolism and growth of the body's cells is called *methionine*. Methionine is found in meat, fish, and dairy products, and it plays an important role in many cell functions. The MTHFR enzyme also plays an important cellular role by converting *homocysteine* into *methionine*. As in normal folate metabolism a genetic mutation of MTHFR is can also result in the body's cells' inability to convert *homocysteine* into *methionine,* leading to a cellular deficiency.

Supplemental *Methionine* is used to prevent liver damage in acetaminophen (Tylenol) poisoning. It is also used for increasing the acidity of urine, treating liver disorders and improving wound healing. Other uses have included treating depression, alcoholism, allergies, asthma, copper poisoning, schizophrenia, drug withdrawal, and Parkinson's disease.

Treatment for Elevated Homocysteine:

A. Lifestyle:

1. Exercise regularly
2. Avoid smoking
3. Avoid excess coffee
4. Avoid alcohol

B. Dietary:

1. Eat an adequate amount of folate-rich green vegetables
2. Follow a Mediterranean/Paleo/Vegetarian Diet
3. Avoid foods fortified with *synthetic* folic acid

C. Supplements & Daily Dosage

1.	5-L-Methylfolate or 5-L-MTHF (active form of folate)	1- 5 mg.
2.	Peroxal-5-phosphate (active form of B6)	25-50 mg.
3.	Methylcobalamin (active form of B12)	1- 4 mg.

D. Indications:

1. Elevated Homocysteine (Hyperhomocysteinemia)
2. Peripheral neuropathies
3. Chronic pain syndromes
4. Chronic fatigue
5. Fibromyalgia

E. Prescription and OTC Supplements: (Note: Rx's contain higher doses/capsule than OTC's)

1. **Rx: Rheumate, Metanx**

   These prescription dosages of metafolin are at FDA approved doses containing the biologically active (bioactive) form of 5-L-MTHF. The bioactive form is transported across cell membranes and is necessary to form methionine from homocysteine, thereby reducing homocysteine blood levels. They contain higher doses of 5-L-MTHF and Vit B12 than the OTC doses.

2. **Rx: Folgard**

   Folgard is also FDA approved prescription and contains *synthetic* folate, Vit B6 & Vit B12. This synthetic form of folate must undergo enzymatic reduction by (MTHFR) to become biologically active. Genetic mutations of MTHFR may result in a cell's inability to convert folic acid to bioactive 5-Methylfolate.

3. **OTC Products** (Containing *5-L-methylfolate, Vit B12 & Vit B6)*
   - **HomocysteineX** (*Seeking Health*)
   - **L-MethylFolate** (Metafolin) (*BioActiv Health*)

4. **TMG (trimethyl-glycine)**

   TMG is a nutrient supplement that is synergistic along with methylfolate & Vit B12. In some cases, a patient will not achieve effective lowering of their homocysteine level with 5-MTHF alone. TMG provides extra methyl groups for the methylation of homocysteine to methionine pathway. When there is no MTHFR mutation, TMG may lower homocysteine levels as a stand alone supplement.

5. **N-Acetyl-cysteine (NAC)**

   NAC supports homocysteine metabolism by mobilizing (separating) the homocysteine molecule from its binding proteins (albumin). N-Acetyl-cysteine at 600 mg daily has also been shown to reduce plasma homocysteine levels.

REFERENCES

- **Metafolin--Alternative for Folate Deficiency Supplementation in pregnant women.** Ginekol Pol. 2013 Jul;84(7):641-6.

  Abstract:

  Proper folate supplementation is required in order to ensure proper folate concentration in the organism, and consequently to prevent the development of numerous complications in general population and pregnant women. **Metafolin** (stable calcium salt of L-5-methyltetrahydrofolate or L-5-MTHF) is the most active form of reduced folate circulating in plasma, which directly enters the metabolic process of folate. After administration metafolin shows optimum absorption, comparable or higher bioavailability as well as physiological activity when compared to folic acid. Metafolin supplementation is effective in decreasing plasma homocysteine, as well as increasing folate in plasma and erythrocytes, in pregnant and breastfeeding women or those who wish to conceive. In addition, metafolin administration omits the multistage process of reduction before entering the folate cell cycle, as well as a possible deficiency of activity of enzymes participating in the reduction of folate process in the intestine epithelium (DHFR and MTHFR enzymes). So far no potential adverse and toxic effects of metafolin management have been reported.

- www.mthfr.net
- www.rawlins.org/mthfr/mthfr.html