



## Homocysteine and *MTHFR* Mutations

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Homocysteine is a chemical in the blood. It is formed when the amino acid methionine, which is a building block of the proteins in our food and body, is naturally broken down (ie, metabolized) to be excreted in the urine (Figure). During this breakdown process, homocysteine can be recycled by our body to be reused to build other proteins. For this recycling, we need vitamins B<sub>12</sub>, B<sub>6</sub>, and folate. If a person is deficient in vitamin B<sub>12</sub>, B<sub>6</sub>, or folate, homocysteine cannot be efficiently recycled and therefore accumulates in the blood. Also, for recycling to be the most efficient, the enzyme methylenetetrahydrofolate reductase (*MTHFR*) is needed. Inherited mutations in the gene that make the *MTHFR* enzyme can lead to an enzyme that is not optimally active and, consequently, may lead to elevated homocysteine levels. Mild to moderate homocysteine elevations are common; extremely high homocysteine elevations are uncommon.

### Background

People with a rare genetic condition called homocystinuria have a defective enzyme that causes homocysteine to accumulate to high levels in the blood.

The disorder was first described in 1962. Individuals with homocystinuria develop severe cardiovascular (affecting heart and blood vessels) disease in their teens and twenties, in addition to a variety of skeletal and neurological-developmental abnormalities and eye problems. This led to the discovery that elevated homocysteine levels are a risk factor for developing blood clots in the arteries and veins and atherosclerosis (hardening of the arteries). Many people in the general population have mildly or moderately elevated homocysteine levels, termed homocysteinemia. This may be due to inherited mutations in the *MTHFR* gene; such mutations are very common. Other causes for elevated levels exist (Table 1). Over the past 20 years, there has been a great deal of research examining the relationship between mild to moderate elevations in homocysteine, and *MTHFR* mutations and the risk for cardiovascular disease and blood clots, as well.

### Homocysteine

#### How Is Homocysteine Measured? What Is a Normal Level?

Homocysteine is measured through a blood test. It is typically not required

for a person to be fasting for the blood draw. There are slightly variable classifications for what is considered an elevated homocysteine level, because normal and abnormal values are set by individual laboratories. Typically, a level <15 μmol/L is considered normal; sometimes the upper limit of normal is given as 14, sometimes as 13 μmol/L. A level between 15 and 30 μmol/L is considered mildly elevated, between 30 and 60 μmol/L is considered moderately elevated, and >60 μmol/L is considered severely elevated. Elevated levels are common: up to 5% to 7% of the general population has a mildly elevated homocysteine level. Individuals with the rare homocystinuria typically have levels of >100 μmol/L.

#### What Are the Risks for Someone With Elevated Homocysteine Levels?

- Cardiovascular disease. Elevated homocysteine levels are associated with an increased risk for cardiovascular disease (see Table 2). The higher the level, the higher the risk. Cardiovascular disease can lead to coronary artery disease, heart attacks, and strokes.

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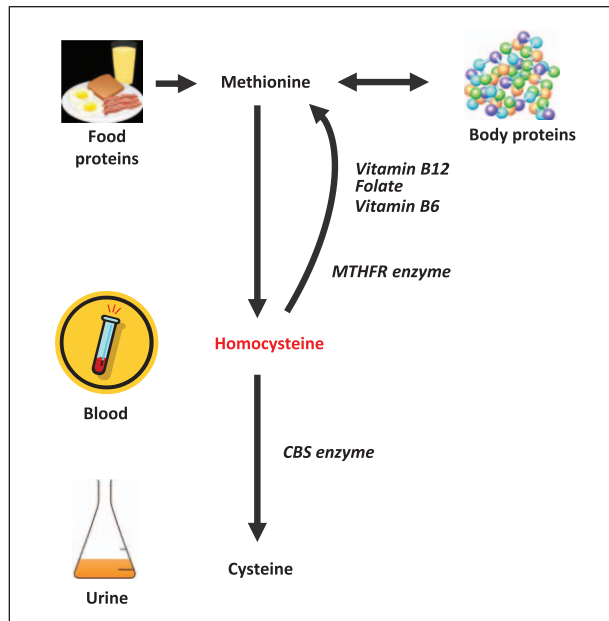
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MTHFR = Methylene-Tetra-Hydro-Folate-Reductase; CBS = Cystathionine-beta-synthase

**Figure.** Homocysteine pathway: breakdown and recycling. CBS indicates cystathionine- $\beta$ -synthase; and MTHFR, methylenetetrahydrofolate reductase.

However, data show that the risk is only mildly increased; in 2010, the American Heart Association issued a statement that it does not consider high homocysteine levels in the blood to be a major risk factor for cardiovascular disease.<sup>1</sup>

b. Clots in veins. Elevated homocysteine levels are associated with an increased risk for blood clots in the veins. Clots in the veins can occur in the extremities, mostly the legs, and are called deep vein thrombosis (DVT); they can also occur in the lung and are called pulmonary

embolism (PE). The higher the homocysteine level, the higher the risk. However, (1) overall, the risk DVT and PE is only slightly increased, and (2) although elevated homocysteine is a risk factor for a first episode of DVT or PE, it does not predict a higher risk of recurrent clot once a patient is off blood thinners. Therefore, finding an elevated homocysteine does not influence the duration a patient should be treated with blood thinners.

**Table 1. Causes of Elevated Homocysteine**

- Dietary deficiency of folic acid, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub>
- Genetic abnormalities, including *CBS* and *MTHFR* mutations
- Low levels of thyroid hormones (hypothyroidism)
- Kidney failure
- Chronic conditions and diseases (such as obesity, high blood pressure, diabetes mellitus, smoking, physical inactivity, high cholesterol)
- Medications (such as atorvastatin, fenofibrate, methotrexate, and nicotinic acid)
- Unknown

**Table 2. Risks That Have Been Associated With Elevated Homocysteine Levels**

- Coronary artery disease (atherosclerosis)
- Heart attack
- Stroke
- Peripheral arterial disease
- Venous thrombosis
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
- Having a child with a neural tube defect (ie, spina bifida)
- Pregnancy complications (preeclampsia, placental abruption, pregnancy loss)
- Role of homocysteine has been investigated in many other diseases (see text)

c. Pregnancy complications. Elevated homocysteine levels have been observed more frequently among women with certain pregnancy complications, including preeclampsia (dangerously elevated blood pressure in pregnancy), placental abruption (where the placenta detaches from the uterus), and recurrent pregnancy loss. However, it appears that elevated homocysteine levels may be a consequence of these complications, rather than the cause. Elevated homocysteine levels are observed more commonly among women who have a child with a neural tube defect (an abnormality of the fetal spine or brain). Neural tube defects include spina bifida (an opening in the fetal spine) and anencephaly (a severe birth defect in which the brain and skull do not form properly). Approximately 20% of women who have a child with a neural tube defect have abnormal homocysteine metabolism. It is recommended that all women of childbearing age take a multivitamin containing 0.4 mg of folic acid per day to reduce the chance of neural tube defects in their children. This recommendation is independent of a person's homocysteine level. A higher dosage of folic acid, usually 4 mg, may be recommended if the woman has had a previous child with a neural tube defect.

d. Others. Homocysteine has been investigated as a risk factor for several other diseases, including autism, cognitive impairment or dementia, depression, Down syndrome, osteoporosis, movement disorders, migraines, multiple sclerosis, and polycystic ovary syndrome. At this time, testing for homocysteine in these contexts is considered investigational.

### How Does Elevated Homocysteine Cause Cardiovascular Disease and Clots in Veins?

It is not clear whether elevated homocysteine causes the blood to clot more

easily, or whether it is just a marker of an increased clotting risk. The observations that homocysteine levels can be effectively lowered by vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, and folic acid, yet that such lowering does not lead to a decrease in cardiovascular disease or venous disease (DVT and PE), suggest that homocysteine is simply a marker of an increased cardiovascular risk, not the cause of it. Accordingly, the American Heart Association in 2010 stated that a causal link between homocysteine levels and atherosclerosis (hardening of the arteries) has not been established.<sup>1</sup>

### Can Homocysteine Levels Be Lowered? If So, How?

Yes, it can be lowered. Folic acid (also referred to as folate), vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> can decrease homocysteine in the blood. A good source for folic acid is fruits and vegetables (especially green leafy vegetables), and fortified breads and cereals, lentils, chickpeas, asparagus, spinach, and most beans, as well. Daily intake of pills containing folic acid, vitamin B<sub>6</sub>, vitamin B<sub>12</sub>, or a combination of the 3 can lower homocysteine levels.

### Who Should Have Their Homocysteine Levels Tested?

The only group of people in whom testing appears indicated are young individuals, such as <20 or 30 years of age, who have had an unexplained heart attack, stroke, DVT, or PE, who are being evaluated for the rare homocystinuria, particularly if additional physical abnormalities suggestive of homocystinuria are present.

Current evidence does not suggest a benefit to testing homocysteine levels in other groups. The US Preventive Services Task Force and the American Academy of Family Physicians have both concluded that there is insufficient evidence to screen asymptomatic adults with no history of coronary heart disease to prevent coronary heart disease events.<sup>2,3</sup> Furthermore, testing is also not beneficial in patients who have coronary artery disease or who have had heart attacks or strokes, because

the lowering of homocysteine levels does not change the risk of future recurrent events. Expert organizations, such as the Thrombosis Interest Group of Canada, have stated that “at the present time, testing for hyperhomocysteinemia in patients with cardiovascular disease or venous thromboembolism (DVT and PE) is not recommended. Testing for MTHFR mutations is not recommended. These tests should not be part of a thrombophilia screening panel.”<sup>4</sup>

### If I Have Elevated Homocysteine, Should I Be Treated?

No. Although taking a daily supplement of folic acid, vitamin B<sub>6</sub>, or vitamin B<sub>12</sub> can effectively lower blood homocysteine levels, such lowering does not lead to a decreased risk of cardiovascular disease, DVT, or PE. Therefore, at the present time, such supplementation with folic acid, vitamin B<sub>6</sub>, or vitamin B<sub>12</sub> for primary prevention of cardiovascular disease is not recommended. Similarly, treating patients with elevated homocysteine and cardiovascular disease or DVT or PE is also not recommended.

## MTHFR Mutations

### Background

Some people develop an elevated homocysteine level, in part, because of a genetic predisposition. People with milder elevations in homocysteine may have a mutation in a gene called *MTHFR* (Figure). The *MTHFR* gene normally produces an enzyme that helps regulate homocysteine levels in the body. We all have 2 *MTHFR* genes, 1 inherited from each parent. Some people have a genetic mutation in 1 or both of their *MTHFR* genes. People with a mutation in 1 *MTHFR* gene are said to be heterozygous; if mutations are present in both genes, the person is said to be homozygous or compound heterozygous for the mutation(s).

### How Common Are MTHFR Mutations?

The most common *MTHFR* mutation is called the *MTHFR* C677T mutation.

The mutation is extremely common in certain ethnic and geographic populations. In the United States, ≈20% to 40% of white and Hispanic individuals are heterozygous for *MTHFR* C677T. The mutation is less common in blacks (1%–2%). In North America, Europe, and Australia, ≈8% to 20% of the population have 2 *MTHFR* C677T mutations, that is, they are homozygous. In people who are heterozygous for an *MTHFR* C677T mutation, there is reduced enzyme function—≈65% of normal. In people who are homozygous for *MTHFR* C677T, there is only 30% of normal enzyme function.

Another mutation called *MTHFR* A1298C is found in 7% to 12% of North American, European, and Australian populations and is less common in Hispanics (4%–5%), Chinese (1%–4%), and Asians (1%–4%). Being homozygous for *MTHFR* A1298C leads to 60% of normal enzyme function. People may also have 1 abnormal *MTHFR* C677T gene plus 1 abnormal *MTHFR* A1298C gene; this is termed double heterozygous. Decreased enzyme function may also result.

### Consequences of Having an MTHFR Mutation

- Cardiovascular disease, DVT and PE, pregnancy complications. Although having a reduced enzyme function of *MTHFR* can lead to elevated homocysteine levels, it does not necessarily do so; many people have normal homocysteine levels, particularly in countries like the United States where food is fortified with folic acid. The *MTHFR* mutations by themselves, in the absence of elevated homocysteine levels, are not a risk factor for cardiovascular disease or DVT and PE in countries where food is fortified with folic acid. They are not clotting disorders (thrombophilias). They do not lead to and are not associated with pregnancy complications, such as pregnancy loss, preeclampsia, and placental abruption.
- Other disorders. Over the past 15 years, a number of studies

have looked at *MTHFR* mutations and the risk of various disorders. At the time of this writing, 615 medical disorders had been researched, with most of the work relating to homocysteine levels, thrombosis, and cardiovascular disease risk, cancer risk, neural tube defects, pregnancy complications, and psychiatric disease. To date, the studies have been conflicting, with some showing that *MTHFR* mutations are related to these additional disorders, whereas others show no association. Often, the results have depended on the ethnicity and geographic location of the population studied, indicating that the effects may be influenced by other genetic or environmental factors.

### Who Should Be Tested for *MTHFR* Mutations?

There is no indication for *MTHFR* mutation testing in routine clinical practice in any patient group. In 2013, the American College of Medical Genetics recommended that *MTHFR* genetic testing should not be ordered as part of the clinical evaluation for risk of blood clots or recurrent pregnancy loss.<sup>5</sup> They recommended 0.4 mg of folic acid per day for all women of childbearing age, regardless of *MTHFR* status, to reduce the risk of neural tube defects. Similarly, in 2013, the American College of Obstetricians and Gynecologists recommended not to screen women for homocysteine or *MTHFR* “because of the lack of association between the *MTHFR* C677T polymorphism and any negative pregnancy outcomes, including any increased risk for DVT and PE.”<sup>6</sup>

### If I Have a *MTHFR* Mutation, Should I Be Treated?

No. The patient with DVT or PE, cardiovascular disease, or pregnancy complication who has, inconsistent with existing professional and evidence-based guidelines, been tested for *MTHFR* mutations and found to have

1 or 2 of these mutations, should be treated the same way as patients who do not have the mutations. The presence of *MTHFR* mutations does not require any special treatment, such as supplementation with folic acid, vitamin B<sub>6</sub>, or vitamin B<sub>12</sub>, and no additional concerns arise.

### Commonly Asked Questions

- “I have had a DVT or PE – should I be tested for homocysteine or *MTHFR*?” No. Although elevated homocysteine is a marker for an increased risk for DVT and PE, finding elevated levels does not influence management. *MTHFR* mutations are not clotting disorders (thrombophilias).
- “I have had a DVT or PE, and my doctor did test me and found that my homocysteine is elevated. Should I take folic acid, vitamin B<sub>6</sub>, and B<sub>12</sub> or a combination of the three?” No. Although taking such supplements effectively lowers homocysteine, it does not lower the risk of recurrent clots.
- “I was tested and found to have an *MTHFR* mutation. What now?” Finding an *MTHFR* mutation has no clinical implications for the patient. It does not explain why the person developed a blood clot or pregnancy complications and does not influence treatment. *MTHFR* mutations are not a clotting disorder (thrombophilia), and testing should not be included in thrombophilia testing panels.
- “I was found to have an *MTHFR* mutation. Should my family members be tested for it?” No. Finding a mutation in family members would not predict adverse medical outcomes (cardiovascular disease, DVT, PE) and would/should not change management.
- “I have had unexplained pregnancy losses and have been found to have elevated homocysteine? Anything I should do differently during a future pregnancy?” No. Any woman, independent of her

homocysteine level and *MTHFR* status, should take folic acid during pregnancy (contained in prenatal vitamin tablets).

- “I have had unexplained pregnancy losses, preeclampsia, or placental abruption and have been found to have *MTHFR* mutations. What does that mean for a future pregnancy?” It has no consequence. Like any other woman, the woman with *MTHFR* mutations should take a prenatal vitamin tablet containing folic acid (0.4 mg) every day throughout pregnancy.

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### Disclosures

None.

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