Homocysteine is a chemical in the blood that is produced when an amino acid (a building block of protein) called methionine is broken down in the body. We all have some homocysteine in our blood. Elevated homocysteine levels (also called hyperhomocysteinemia) may cause irritation of the blood vessels. Elevated levels of homocysteine show an increased risk for (1) hardening of the arteries (atherosclerosis), which could eventually result in a heart attack and/or stroke, and (2) blood clots in the veins, referred to as venous thrombosis.

The purpose of this Cardiology Patient Page is to explain the relation between elevated homocysteine levels and blood clots in the arteries and veins; to discuss the causes of elevated homocysteine levels, including common genetic variants in the MTHFR gene (see the “What Do I Need to Know About a Hereditary Predisposition?” section); and to describe ways to monitor and lower homocysteine levels to possibly improve health.

Historical Perspective
In 1962, it was reported that people with a rare genetic condition called homocystinuria were prone to develop severe cardiovascular disease in their teens and 20s. In this condition, a defective enzyme causes an accumulation of homocysteine in the blood, resulting in very high levels. Studies of children with homocystinuria led to the discovery that elevated homocysteine levels are a risk factor for developing atherosclerosis and blood clots in the arteries and veins. Although homocystinuria is a rare disease (affecting about 1 in 200,000 people), many more people have mildly or moderately elevated homocysteine levels.

Causes of Elevated Homocysteine Levels
Some people have elevated homocysteine levels (Table 1) caused by a deficiency of B vitamins and folate in their diets. High homocysteine levels are also seen in people with kidney disease, low levels of thyroid hormones, psoriasis, and with certain medications (such as antiepileptic drugs and methotrexate). It has been recognized that some people have a common genetic variant (called methylenetetrahydrofolate reductase, abbreviated MTHFR) that impairs their ability to process folate. This defective gene leads to elevated levels of homocysteine in some people who inherit MTHFR variants from both parents.

How Is Homocysteine Measured?
Homocysteine is measured through a routine blood test. Most of the time, no
preparations are needed before blood testing. Occasionally, a practitioner may order a fasting homocysteine level, which requires fasting for 10 hours before the blood draw. Fasting before the blood draw is probably not necessary, as short-term dietary factors will not likely influence test results.

Occasionally, a practitioner may order a test called the methionine-load test. This test measures homocysteine levels before and after the intake of 100 mg/kg of methionine (dissolved in orange juice). The test is most commonly used to diagnose abnormal homocysteine metabolism in people who have a high risk for cardiovascular disease but who have normal baseline homocysteine levels. This test can be used to make decisions about therapy, as people with abnormal “load” tests may respond better to vitamin B6 supplementation compared with folic acid.

What Is Considered An “Elevated” Homocysteine Level?

There are somewhat variable classifications for what is considered an elevated homocysteine level. “Normal” and “abnormal” values are set by individual laboratories. Typically, a level less than 13 μmol/L is considered normal. A level between 13 and 60 μmol/L is considered moderately elevated, and a value greater than 60 to 100 μmol/L is severely elevated.

How Does an Elevated Homocysteine Level Lead to Blood Vessel Damage and Thrombosis?

Although we know that elevated homocysteine levels are observed more often in people with thrombosis and atherosclerosis, it is unclear whether it is the homocysteine itself that leads to the damage or whether the elevation of homocysteine is a result of the damage. Recent studies show that lowering homocysteine levels does not decrease the risk for atherosclerosis or thrombosis; this supports the theory that homocysteine may just be an “innocent bystander” and not the cause of these conditions. Furthermore, it is poorly understood how homocysteine might exert damaging effects. A hypothesis is that homocysteine has a toxic effect on the cells that make up the innermost layer of blood vessels. Further studies are needed to clarify the role of homocysteine in atherosclerosis and thrombosis and to determine whether lowering the homocysteine level is effective in decreasing the risk for blood clots.

What Are the Risks for Someone With Elevated Homocysteine Levels?

An elevated homocysteine level is associated with an increased risk for developing atherosclerosis, which can in turn lead to coronary artery disease (CAD), heart attack, and stroke (Table 2). The magnitude of risk for CAD is not well defined. Generally, it seems that people with an elevated homocysteine level may have about twice the risk of CAD compared with those without a high homocysteine level. However, the risk is dependent on the homocysteine level. For example, in one study, researchers found that for every 10% elevation in homocysteine, there was nearly the same rise in the risk of CAD. The risk may also be related to how long someone has had an elevated homocysteine level.

There is also an increased likelihood of having a blood clot in the veins of the body if you have an elevated homocysteine level. A clot in the veins is called a venous thrombosis. Most often, venous thrombosis occurs in the legs; however, the clot can break away from the wall of the vein and travel to the lung, leading to a potentially fatal complication called pulmonary embolism (see also Cardiology Patient Pages5,6). Venous blood clots occur in approximately 1 in 1000 individuals per year. Certain studies have suggested that elevated homocysteine levels roughly double the risk of developing venous thrombosis.

It has been recognized that elevated homocysteine is associated with dementia, particularly Alzheimer’s disease. How homocysteine is related to dementia is not yet fully understood. It is suspected that there is a connection between homocysteine levels and blood vessel changes in the brain. Research in this area is ongoing.

Women’s Health

There are certain implications of having elevated homocysteine that are specifically relevant for women. Elevated homocysteine levels have been observed more frequently among women with certain pregnancy complications, including preeclampsia (elevated blood pressure that can lead to dangerous consequences), placental abruption (where the placenta detaches from the uterus), recurrent pregnancy loss, and giving birth to a small, low-birth-weight baby (called intrauterine growth restriction). However, medical research suggests that elevated homocysteine levels may be a consequence of these complications, rather than the cause.

Hyperhomocysteinemia is 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.
TABLE 3. Therapy for Elevated Homocysteine Levels: Individual Tablets

<table>
<thead>
<tr>
<th>Name</th>
<th>Folic Acid</th>
<th>Vitamin B6</th>
<th>Vitamin B12</th>
<th>No. of Tablets per Day Needed</th>
<th>Approximate Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₁₂</td>
<td>50 mg</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>$1.00</td>
</tr>
<tr>
<td>Folic acid</td>
<td>0.8 mg (=800 μg)</td>
<td>...</td>
<td>...</td>
<td>3</td>
<td>$1.50</td>
</tr>
<tr>
<td>Total per month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$4.00</td>
</tr>
</tbody>
</table>

There are many tablet strengths. Be sure to read the label and find the correct strength.

Does Lowering Homocysteine Levels Decrease the Risk for Atherosclerosis and Thrombosis?

It is not clear whether lowering homocysteine levels actually decreases the risk for atherosclerosis and thrombosis. So far, only 2 clinical studies have been published on this issue. Although in these studies folic acid and vitamin B complex (made up of vitamins B₆ and B₁₂) were successful in lowering homocysteine levels, no clinical benefit was seen; ie, the lowering of homocysteine levels did not result in fewer heart attacks, strokes, or vascular blood clots. This lends support to the notion that homocysteine may not be the cause of thrombosis and atherosclerosis but rather a byproduct of blood vessel damage that occurs through other mechanisms. One could therefore argue that there is no reason to treat elevated homocysteine levels, and this is perhaps true. However, at this point, many practitioners recommend treating elevated homocysteine levels because (1) it is still possible that an elevated homocysteine level contributes to the risk for thrombosis and atherosclerosis and that lowering its level is beneficial and (2) treatment with folic acid and vitamins B₆ and B₁₂ appears to be safe. More research is needed to determine whether lowering homocysteine levels has any benefit. At this point, it is important that patients (and practitioners) do not overrate the importance of folic acid and vitamin B complex therapy.

How Can You Lower Homocysteine Levels?

Elevated homocysteine levels can be lowered. We know that folic acid, vitamin B₆, and vitamin B₁₂ are all involved in breaking down homocysteine in the blood. Therefore, increasing your intake of folic acid and B vitamins may lower your homocysteine level. A good source of folate can be found in fruits and vegetables (especially green leafy vegetables). Other good sources of folate include fortified breads and cereals, lentils, chickpeas, asparagus, spinach, and most beans.

If adjusting your diet does not lower your homocysteine to the desired level, specific vitamins are often effective. Over-the-counter multivitamins that contain at least 250 μg (0.25 mg) of folic acid, as well as vitamins B₆ and B₁₂ (usually 2 to 25 mg for B₆ and 5 to 100 μg for B₁₂) may be effective. However, they may not be sufficient, because they only contain relatively low amounts of folic acid, vitamin B₆, and vitamin B₁₂. A better option is to purchase folic acid, vitamin B₆, and vitamin B₁₂ supplements separately.

This involves taking several different tablets a day, but it is a relatively inexpensive method. The dosing of folic acid and vitamins B₆ and B₁₂ can be confusing. Table 3 helps shed some light on the appropriate doses. Last, your doctor can prescribe medications that contain higher levels of folic acid and B vitamins. These are convenient combination pills (Table 4) that make the confusing search in the drug store for tablets with the right doses obsolete. High amounts of these vitamins are not known to pose any health hazards.

Women considering pregnancy should discuss their elevated homocysteine levels with a doctor. 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. A higher dosage of folic acid, usually 4 mg, may be recommended if you have elevated homocysteine levels before pregnancy.

How Often Should Homocysteine Levels Be Checked?

Once an elevated level has been found and folic acid and/or vitamin B₆ and B₁₂ therapy is initiated, it is worthwhile to recheck a level about 2 months later to make sure that it has normalized. If it has not normalized, the dose of folic acid or vitamin B₆ and B₁₂ can be increased. It is reasonable to then recheck levels another 2 months later.

What Do I Need to Know About a Hereditary Predisposition?

Some people develop an elevated homocysteine level in part because of a genetic predisposition. The MTHFR gene mentioned previously produces an enzyme that helps regulate homocysteine levels in the body. If there is a genetic error (called a mutation) in the MTHFR gene, homocysteine levels may not be regulated properly. Genetic mutations in MTHFR are the most commonly known inherited risk factor for elevated homocysteine levels. We

TABLE 4. Therapy for Elevated Homocysteine Levels: Combination Tablets

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Folic Acid</th>
<th>Vitamin B₆</th>
<th>Vitamin B₁₂</th>
<th>Approximate Monthly Cost</th>
<th>Generic Available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Folbee*</td>
<td>2.5 mg</td>
<td>25 mg</td>
<td>1000 μg</td>
<td>$12.50</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Folgard Rx 2.2</td>
<td>2.2 mg</td>
<td>25 mg</td>
<td>500 μg</td>
<td>$14.00</td>
<td>No</td>
</tr>
<tr>
<td>Foltx</td>
<td>2.5 mg</td>
<td>25 mg</td>
<td>1000 μg</td>
<td>$21.00</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Generic for Foltx.
all have 2 MTHFR genes, one inherited from each parent. Some people have a genetic mutation in one or both of their MTHFR genes. People with mutations in one MTHFR gene are called “heterozygous” for the MTHFR mutation; if mutations are present in both genes, the person is said to be “homozygous” for the mutation.

The most common MTHFR mutation is called the MTHFR C677T mutation, or the “thermolabile” MTHFR mutation. Another common mutation is called MTHFR A1298C. To have any detrimental effect, mutations must be present in both copies of a person’s MTHFR genes. Having only one mutation, ie, being heterozygous, is, from a medical perspective, irrelevant. Even when 2 MTHFR mutations are present (eg, 2 C677T mutations, or one C677T mutation and one A1298C mutation), not all people will develop high homocysteine levels. Although these mutations do impair the regulation of homocysteine, adequate folate levels essentially “cancel out” this defect.

Are Treatments Different for People With a Hereditary Predisposition to Elevated Homocysteine?

Regardless of whether you have an MTHFR mutation in both genes or not, the treatment for elevated homocysteine is the same—dietary intervention and supplementation with folic acid and vitamins B6 and B12. The amount of each of these supplements should be adjusted on the basis of the degree of homocysteine elevation, not your genetic status. If you have mutations in both MTHFR genes but have normal homocysteine levels, you do not need to be on folic acid or vitamin B6 or B12 therapy.

Are There Any Other Implications of Having MTHFR Mutations?

Studies have been conducted to investigate whether having 2 MTHFR mutations increases the risk of blood clots in the arteries, blood clots in the veins, or CAD.9,10 Overall, evidence from these studies indicates that, so long as the homocysteine level is normal, MTHFR mutations do not significantly increase the risk of heart attack or stroke. Studies investigating the association of MTHFR mutations and venous blood clots have been inconsistent, with some studies showing a slight association, but most studies have not shown any association. Although a few studies have suggested that MTHFR mutations may interact with other inherited risk factors for clotting disorders (such as a gene mutation called factor V Leiden; see also Cardiology Patient Page11), most studies show that the MTHFR mutations do not further increase the clotting risk associated with factor V Leiden.

MTHFR mutations have been linked in some studies to an increased chance of having a baby with a neural tube defect (spina bifida).9 One study suggested that mothers with 2 MTHFR mutations were twice as likely to have a baby with a neural tube defect, whereas other studies have not supported this finding. Recent research has implied that risks vary, based on the nutritional status of the mother (ie, folate levels, vitamin intake) and whether or not she has an elevated homocysteine level.12 Because of this controversy, some practitioners may recommend extra folate supplementation (usually 4 mg) for women with 2 MTHFR mutations, whereas other practitioners will recommend normal use of prenatal vitamins containing folic acid for a woman who does not have an elevated homocysteine level.

There is also conflicting evidence about the relation between homozygous MTHFR mutations and pregnancy complications (including pre-eclampsia, placental abruption, recurrent pregnancy loss, and intrauterine growth restriction, as described earlier). A recent meta-analysis, which combined all of the data from these studies, found that there was not an association between MTHFR and recurrent pregnancy loss.13 It seems that homozygous MTHFR may moderately increase the risk of preeclampsia and placental abruption, but more research in this area is necessary. Although it is not standard medical practice to test for MTHFR mutations when a woman has a history of these complications, some practitioners may order this testing.

Who Should Be Tested for Homocysteine Levels and Who for MTHFR Mutations?

For homocysteine, no official guidelines exist as to who should be tested. Having blood homocysteine levels checked appears appropriate in individuals with unexplained blood clots (arterial or venous) and unexplained atherosclerosis. One can also argue that everybody with atherosclerosis, ie, patients with CAD, heart attacks, or strokes, should have their blood homocysteine value checked. At this time, it is not clear whether women with a history of recurrent pregnancy loss, pre-eclampsia, placental abruption, and/or small-for-age babies should have homocysteine levels checked.

For MTHFR, as with homocysteine testing, no official guidelines exist as to who should be tested. In the absence of elevated homocysteine levels, MTHFR mutations appear to have no clinical relevance in regard to thrombosis and atherosclerosis. Therefore, one could argue that there is no indication to perform MTHFR genetic testing. The authors of this article take this approach in their clinical practice. It may, however, be reasonable to check mothers who gave birth to a baby with spina bifida for the MTHFR mutations.

Summary

Having elevated homocysteine levels indicates an increased risk of CAD and blood clots in the arteries and veins. You can lower elevated levels by taking folic acid, vitamin B6, and vitamin B12, or a combination of the 3. However, recent studies indicate that lowering an elevated homocysteine level does not decrease the risk of atherosclerosis and blood clots. Until this issue has been more clearly
defined, it appears prudent to make an effort to try to lower one’s homocysteine levels through supplementation with folate and B vitamins. An individual should develop a plan with his/her physician to check homocysteine levels periodically and adjust treatment accordingly. Women with elevated homocysteine levels should also be aware of the possible implications that this may have for pregnancy complications and should discuss this with a knowledgeable healthcare provider. The MTHFR mutations appear to be medically irrelevant, so long as an individual’s homocysteine level is normal. Therefore, it should be the homocysteine level, not the MTHFR genetic status, that is tested in patients with or at risk for blood clots, atherosclerosis, or pregnancy complications.

References

Additional Resources
Homocysteine and MTHFR Mutations: Relation to Thrombosis and Coronary Artery Disease

Elizabeth A. Varga, Amy C. Sturm, Caron P. Misita and Stephan Moll

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