

Thrombophilia: Homocysteinemia and Methylene Tetrahydrofolate Reductase



Thrombosis Canada
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Objective:

- To review the clinical relevance of testing for homocysteinemia and methylene tetrahydrofolate reductase (MTHFR) gene mutations.
- To discuss the evidence for reducing homocysteine levels for vascular protection and prevention of venous thromboembolism (VTE).

Background:

Homocysteine is an amino acid not found in food but obtained from the conversion of dietary methionine. Homocysteine can be converted back into methionine or metabolized into cysteine through pathways involving several enzymes and the cofactors folic acid, vitamin B12 and vitamin B6. Normal plasma concentrations of homocysteine range from 5-15 $\mu\text{mol/L}$.

Mild to moderate hyperhomocysteinemia ranging between 15-30 $\mu\text{mol/L}$ is common and can be seen in 5-12% of the general population. The causes of mild to moderate elevations in homocysteine include enzyme defects, renal insufficiency, hypothyroidism, alcoholism, some drugs (such as methotrexate, phenytoin, carbamazepine, isoniazid), and deficiencies of vitamin B12 or folic acid. These levels of homocysteine are associated with atherosclerosis and increased risk of stroke, ischemic heart disease and peripheral arterial disease. Observational studies have shown an inconsistent or weak association with first episode or recurrent VTE. Hyperhomocysteinemia has been associated with obstetric complications but the importance and significance of this association remain unclear.

Methylene tetrahydrofolate reductase (MTHFR) gene mutation is one of the most common enzymatic defects that may lead to elevation of homocysteine levels. MTHFR is required for the regeneration of methionine from homocysteine. The genetic mutation, which results from a single nucleotide substitution at position 677 (C677T), produces a form of MTHFR that has decreased activity. As a consequence, homocysteine cannot be reconverted to methionine, and homocysteine levels increase. Approximately 40% and 10% of the general population are heterozygous carriers and homozygous for this mutation, respectively. The significance of the MTHFR mutation in the absence of hyperhomocysteinemia is unclear.

Homocystinuria is a rare genetic disease that is usually diagnosed in childhood. It causes very high levels of homocysteine and severe clinical manifestations including premature vascular disease and VTE. This condition is not addressed in this guide.

Diagnosis:

VTE:

It is unclear if identifying individuals with hyperhomocysteinemia in the evaluation of VTE is clinically relevant because interventions for decreasing homocysteine level in such individuals do not reduce their risk of first or recurrent VTE. **Therefore, routine testing for hyperhomocysteinemia and MTHFR mutations in patients with VTE is not recommended.**

Cardiovascular outcomes:

The clinical relevance of measuring homocysteine levels is also unclear when evaluating risk of atherosclerotic events. Homocysteine-lowering therapy has not been shown to reduce the risk of myocardial infarction or total cardiovascular death in clinical trials. Reductions in stroke have been demonstrated with B vitamin supplementation. Patients with normal levels of homocysteine were not excluded in all trials, but mean baseline levels of homocysteine were elevated. The patients in these trials had other traditional cardiovascular risk factors. Testing for MTHFR mutations is not recommended.

Management:

B vitamin supplementation (folic acid, vitamin B6, and vitamin B12, either alone or in some combination) may lower homocysteine levels within a few weeks. However, clinical trials have not demonstrated that decreasing the levels of homocysteine reduces **recurrent VTE**, even in patients with high baseline levels. Based on currently available data, treating hyperhomocysteinemia **in patients with VTE** is not recommended.

B vitamin supplementation has also not demonstrated benefit in reducing myocardial infarction or cardiovascular death. There has been a suggestion that B vitamin supplementation may reduce the risk of stroke, particularly if a patient has an eGFR above 50 mL/min/1.73m²; however, a benefit has not been conclusively demonstrated. Furthermore, no benefit in stroke reduction is found when analyzing the subgroup of patients with an eGFR below 50 mL/min/1.73m².

B vitamin supplementation for primary prevention of cardiovascular disease is also not recommended in areas where there is prevalent folate-fortification of grains. In regions where folate-fortification of grains is uncommon, then vitamin supplementation can be considered in those patients with other atherosclerotic risk factors with the aim of reducing risk of stroke. The Chinese Stroke Prevention Trial (CSPT), a primary prevention study conducted in China on subjects for whom folic acid supplementation had not been implemented, found a reduction in stroke (0.7% absolute risk reduction) with the addition of folic acid to enalapril in patients with hypertension compared with the use of enalapril alone.

The optimal management of adverse obstetric outcome in patients with hyperhomocysteinemia is not known.

Pediatrics:

The MTHFR mutation in combination with hyperhomocysteinemia is reported to be associated with stroke in children. Pediatricians with expertise in thromboembolism should manage, where possible, pediatric patients with thromboembolism. When this is not possible, a combination of a neonatologist/pediatrician and an adult hematologist, supported by consultation with an experienced pediatric hematologist, is recommended.

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