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# Homocysteine: Is it a clinically important cardiovascular risk factor?

## ■ ABSTRACT

Elevated plasma homocysteine is associated with an increased risk of myocardial infarction, stroke, and venous thromboembolism. Folic acid and other B vitamins lower plasma homocysteine levels, but whether this therapy confers a clinical benefit has yet to be determined. Until we know the results of ongoing clinical trials of homocysteine-lowering therapy, testing for and treating elevated homocysteine is probably justified only in patients with known cardiovascular disease or who are at high risk.

## ■ KEY POINTS

High homocysteine levels are believed to directly increase the risk of cardiovascular disease, but they may actually result from cardiovascular events or merely be markers of cardiovascular disease.

Although homocysteine-lowering therapy has not been proven to lower cardiovascular risk, it is inexpensive and presumed safe.

Homocysteine can be lowered to normal levels in most patients with mildly or moderately elevated levels with either folic acid 0.4 to 5.0 mg/day, vitamin B<sub>12</sub> 0.5 to 1.0 mg/day, or both. The treatment may be less effective in patients with renal disease.

If treatment is undertaken, the goal of therapy should be a homocysteine level of less than 10  $\mu\text{mol/L}$  in patients at high cardiovascular risk.

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**F**OR ALMOST TWO DECADES we have known that a high plasma homocysteine level (hyperhomocysteinemia) is associated with increased cardiovascular risk. But whether elevated homocysteine causes cardiovascular disease or is a consequence of it remains unknown.

Adding folic acid and other B vitamins to the diet is effective in lowering levels, but whether it improves the clinical outlook is also still uncertain and is the focus of several ongoing clinical trials.

In this article, we summarize the causes and clinical manifestations of elevated homocysteine levels, proposed mechanisms linking homocysteine to vascular disease, and indications for testing for and treating hyperhomocysteinemia.

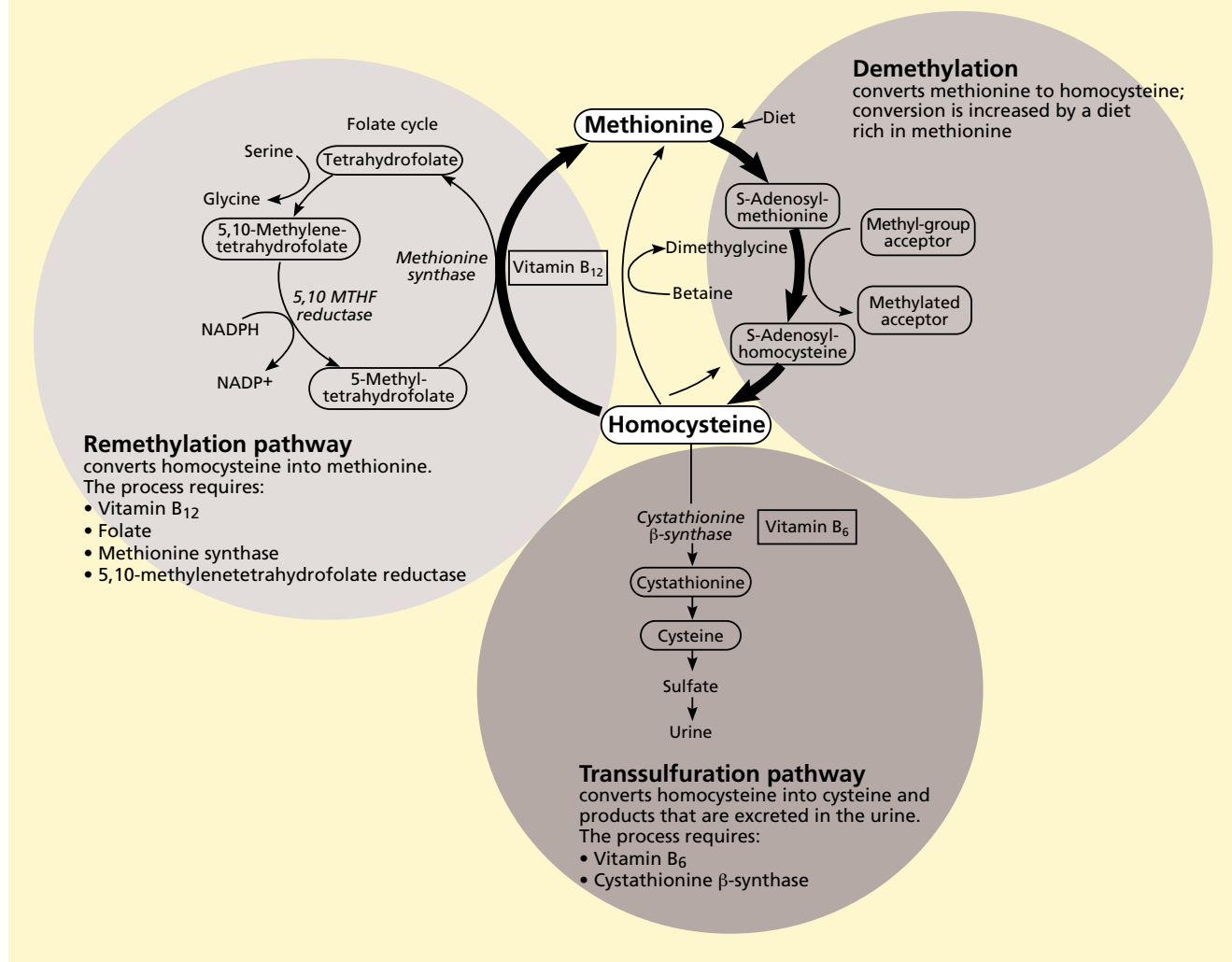
## ■ CAUSES OF HYPERHOMOCYSTEINEMIA

Homocysteine, a sulfur-containing amino acid, is a key intermediate in methionine metabolism (FIGURE 1). It is produced as a byproduct of methyl transfer reactions, which are important for the synthesis of nucleic acids, methylated proteins, neurotransmitters, and phospholipids.<sup>1</sup>

Hyperhomocysteinemia can be caused by genetic defects, nutritional deficiencies, renal dysfunction, alcoholism, hypothyroidism, or certain medications (TABLE 1).

**Severe hyperhomocysteinemia.** People with rare inborn errors of methionine metabolism have very high levels of homocysteine in the plasma ( $> 100 \mu\text{mol/L}$ ) and in the urine and a very high incidence of vascular disease.

## How homocysteine is produced and metabolized



**FIGURE 1**

FROM BALLAL RS, JACOBSEN DW, ROBINSON K. HOMOCYSTEINE: UPDATE ON A NEW RISK FACTOR. CLEVE CLIN J MED 1997; 64:543-549.

This condition, recognized for more than 30 years, is called “hereditary homocystinuria.”<sup>2</sup>

Most cases of severe hyperhomocysteinemia are caused by autosomal-recessive defects in cystathionine beta-synthase, which also cause skeletal deformities, ocular abnormalities, mental retardation, hepatic steatosis, and premature death.<sup>3</sup> Untreated patients have about a 50% chance of having a myocardial infarction, stroke, or venous thromboembolism before age 30.<sup>3</sup>

**Moderate hyperhomocysteinemia** (plasma total homocysteine 30–100 μmol/L) may be seen in patients with moderate vitamin B<sub>12</sub> deficiency, severe folate deficiency, or renal

failure. The cause of hyperhomocysteinemia in renal disease is not well understood, but may involve decreased clearance of homocysteine by the kidneys or extrarenal tissues.<sup>4</sup>

**Mild hyperhomocysteinemia** (plasma total homocysteine 10–30 μmol/L) is common in the general population, especially the elderly.<sup>5,6</sup> It is often caused by renal insufficiency or mild to moderate vitamin B<sub>12</sub> deficiency. Folate deficiency is no longer a common cause of mild hyperhomocysteinemia in the United States and Canada since cereal grains have been fortified with folic acid.<sup>7</sup>

Mild hyperhomocysteinemia may also be caused by genetic factors, including heterozy-



gosity for mutations in the gene for cystathionine beta-synthase or homozygosity for a common polymorphism in the gene that encodes the enzyme 5,10-methylene tetrahydrofolate reductase (*MTHFR*), specifically a C-to-T substitution at base 677 of the gene (*MTHFR* 677 C→T).<sup>8</sup> The clinical value of testing for these mutations has not been proven, and it is unlikely to provide more risk information than the homocysteine level. The *MTHFR* 677 C→T genotype appears to be associated with hyperhomocysteinemia and increased risk mainly in people with low folate intake.<sup>8</sup>

### ■ HOMOCYSTEINE AS A RISK FACTOR

A number of retrospective (case-control and observational) and prospective studies done over the past 15 years indicate that homocysteine is a graded, independent risk factor for myocardial infarction, stroke, and venous thromboembolism.<sup>9–11</sup>

#### What is 'abnormal'?

The normal reference range for plasma total homocysteine is usually defined as the 2.5th to 97.5th percentile interval for presumably healthy people. The lower limit is typically 5  $\mu\text{mol/L}$ , but the upper limit varies considerably among clinical laboratories. Furthermore, in different populations, the upper limit may vary between 10 and 20  $\mu\text{mol/L}$ , depending on age (levels increase with age), sex (levels are higher in men than in women), ethnic group, and dietary intake of folate.<sup>12</sup> Adding to the confusion, mean levels of homocysteine have decreased in the United States since 1998, when enriched flour began to be fortified with folic acid to prevent neural tube defects in newborns.<sup>13</sup>

Rather than defining a level of homocysteine as either normal or abnormal, it may be more useful to consider homocysteine, like cholesterol and C-reactive protein, as a graded risk factor for cardiovascular disease.<sup>14,15</sup> A meta-analysis<sup>16</sup> found that for every 2.5- $\mu\text{mol/L}$  increase in plasma total homocysteine, the risk of myocardial infarction increases by about 10% and the risk of stroke increases by about 20%. The relationship between homocysteine and risk appears to hold for plasma concentrations of total homo-

**TABLE 1**

### Causes of hyperhomocysteinemia

#### Severe hyperhomocysteinemia (> 100 $\mu\text{mol/L}$ )

- Hereditary homocystinuria (eg, homozygosity for defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or other enzymes of methionine metabolism)
- Hereditary disorders of vitamin B<sub>12</sub> utilization
- Severe deficiency of vitamin B<sub>12</sub>

#### Moderate hyperhomocysteinemia (30–100 $\mu\text{mol/L}$ )

- Renal failure
- Moderate vitamin B<sub>12</sub> deficiency
- Severe folate deficiency

#### Mild hyperhomocysteinemia (10–30 $\mu\text{mol/L}$ )

- Heterozygosity for defects in cystathionine beta-synthase
- Homozygosity for the C677T polymorphism of 5,10-methylene-tetrahydrofolate reductase
- Renal insufficiency
- Renal transplantation
- Mild folic acid deficiency
- Mild vitamin B<sub>12</sub> deficiency
- Vitamin B<sub>6</sub> deficiency
- Hypothyroidism
- Alcoholism
- Medications (niacin, fibrates, methotrexate, isoniazid, levodopa, theophylline, phenytoin, nitrous oxide, trimethoprim)

cysteine between 10 and 30  $\mu\text{mol/L}$ .

A more sensitive way to identify people at increased cardiovascular risk may be to measure plasma homocysteine after an oral methionine load. However, methods for administering methionine and collecting samples must be standardized before this can be generally recommended.<sup>12,17</sup>

#### Is homocysteine a consequence, cause, or marker of disease?

It has not been established whether homocysteine is a consequence, a cause, or a marker of cardiovascular disease.

**Consequence?** Evidence that elevated homocysteine may be a consequence of vascular disease is that the relative risk associated with mild homocysteine elevation has tended to be higher in retrospective studies (in which homocysteine was measured after a vascular event) than in prospective studies (in which it was measured before an event).<sup>16</sup>

**Cause?** However, when analysis is limited

to prospective data and adjusted for other risk factors, hyperhomocysteinemia still emerges as a modest but significant risk factor for cardiovascular events.<sup>16</sup> Elevated total homocysteine is also a strong predictor of mortality in patients with preexisting cardiovascular disease or other risk factors.<sup>12,18</sup>

Other evidence that it is a cause is that vascular manifestations are common in patients with severe hyperhomocysteinemia caused either by defects in the cystathionine beta-synthase-dependent transsulfuration pathway that produce elevated levels of both homocysteine and methionine or by defects in the methionine synthase-dependent remethylation pathway that produce elevated levels of homocysteine but not methionine.

In addition, estimates of cardiovascular risk of hyperhomocysteinemia caused by genetic variation in 5,10-methylene tetrahydrofolate reductase, which are relatively free from confounding due to reverse causality,<sup>19</sup> are similar to those estimated from prospective studies of homocysteine levels.<sup>8,15</sup>

Experimental evidence also supports the theory that high homocysteine causes vascular problems: induced hyperhomocysteinemia in animals produces vascular abnormalities, including endothelial dysfunction and vascular hypertrophy, that are very similar to those seen with other risk factors such as hypertension, diabetes, and hypercholesterolemia.<sup>20</sup> Hyperhomocysteinemia also accelerates atherosclerosis progression in apolipoprotein E-deficient mice.<sup>21–23</sup>

In human subjects, acute hyperhomocysteinemia induced by oral methionine loading causes endothelial dysfunction.<sup>24</sup>

Possible mechanisms of hyperhomocysteinemia's vascular effects include impaired release of endothelium-derived nitric oxide, oxidative injury, accelerated atherosclerosis, altered hemostatic balance, endoplasmic reticulum stress, and activation of inflammatory pathways.<sup>25,26</sup>

**Marker?** It is also plausible that the relationship between hyperhomocysteinemia and cardiovascular disease is indirect, and is confounded by other factors (eg, renal insufficiency or deficiencies of folate, vitamin B<sub>12</sub>, or vitamin B<sub>6</sub>) that influence both homocysteine levels and cardiovascular risk.

## ■ CLINICAL MEASUREMENT

Because of increasing interest in hyperhomocysteinemia as a cardiovascular risk factor, most clinical reference laboratories can now measure plasma homocysteine levels. Clinical assays measure total homocysteine, which includes the thiol homocysteine and its protein-bound and free disulfide derivatives.<sup>27,28</sup>

Other than to help predict cardiovascular risk, reasons for measuring homocysteine are to screen for inborn errors of methionine metabolism and as an adjunctive test for vitamin B<sub>12</sub> deficiency.

Blood samples can be collected in either the fasting or nonfasting state. Plasma must be isolated quickly (within 1 hour at room temperature or 8 hours if the sample is kept on ice) to avoid spurious elevation of homocysteine due to leakage from erythrocytes and leukocytes. A reducing agent is added to the sample to convert disulfide forms to homocysteine, which is detected using either chromatographic or immunologic methods. The different methods give comparable results, but certified reference materials are lacking, and standardization is needed to minimize variation among laboratories.<sup>12</sup>

## ■ HOMOCYSTEINE-LOWERING THERAPY

Homocysteine-lowering therapy is life-saving for patients with severe hyperhomocysteinemia due to autosomal-recessive deficiency of cystathionine beta-synthase. Approximately 50% of patients respond to treatment with vitamin B<sub>6</sub> in pharmacological doses.<sup>3</sup> Adjunctive therapy may include methionine restriction, cysteine supplementation, betaine, vitamin B<sub>12</sub>, or folic acid.<sup>29,30</sup> Interestingly, long-term therapy substantially decreases vascular risk despite only partially correcting elevated plasma homocysteine.<sup>30</sup>

In people with mild or moderate hyperhomocysteinemia, B vitamins are highly effective in lowering homocysteine. A meta-analysis of 12 randomized trials performed before folic acid fortification was instituted<sup>31</sup> found that treatment with folic acid 0.5 to 5 mg/day decreased homocysteine levels by 25%, and that the addition of vitamin B<sub>12</sub> 0.5 mg/day decreased homocysteine by another 7%.

**The risk of MI increases about 10% for every 2.5 μmol/L increase in homocysteine**



Adding vitamin B<sub>6</sub> did not improve the homocysteine-lowering effect of folic acid and vitamin B<sub>12</sub>.

Now that cereal grains are fortified with folic acid, additional folic acid supplementation may not work as well. Nevertheless, it is possible to achieve normal levels of plasma homocysteine in most people with mild or moderate hyperhomocysteinemia, although patients with renal failure may be resistant.<sup>32</sup>

### Benefit of therapy uncertain

Several randomized clinical trials are under way in people with coronary heart disease, stroke, or venous thromboembolism to test the effectiveness of homocysteine-lowering therapy with folic acid and vitamin B<sub>12</sub> (with or without vitamin B<sub>6</sub>) in preventing secondary events.<sup>33</sup> Results from most of the trials will not be available until 2005 or 2006, but a few have been completed or reported in preliminary form.<sup>34-42</sup>

Results thus far are mixed. Two trials examined the effect of homocysteine-lowering therapy on the rate of restenosis following percutaneous coronary interventions. One found a lower rate of restenosis in the treated group,<sup>34,35</sup> while the other found treatment to be detrimental.<sup>37</sup> Similar inconsistencies are emerging from other intervention trials.<sup>38-42</sup>

The conflicting results may be partly due to inadequate statistical power,<sup>33</sup> especially in the United States and Canada, where folic acid fortification has decreased homocysteine levels in the control population.<sup>43</sup> This appears to have been a factor in the recent Vitamin Intervention for Stroke Prevention (VISP) trial, which found no effect of homocysteine-lowering therapy on vascular outcomes in patients with prior stroke.<sup>36</sup>

## RECOMMENDATIONS

Given that the jury is still out on the benefit of homocysteine-lowering therapy, should physicians detect and treat hyperhomocysteinemia?

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From a strictly evidence-based perspective, routine screening for hyperhomocysteinemia and prescribing vitamins to lower homocysteine are unwarranted. The American Heart Association<sup>44</sup> and a European expert panel<sup>12</sup> advise against general screening for hyperhomocysteinemia, and the US Preventive Services Task Force has concluded that evidence is insufficient to recommend vitamin supplements to prevent cardiovascular disease.<sup>45</sup>

On the other hand, there is good reason to believe that homocysteine is an independent cardiovascular risk factor and that homocysteine-lowering therapy ultimately may prove to have a modest clinical benefit. Treating with either folic acid 0.4-5.0 mg/day or vitamin B<sub>12</sub> 0.5-1.0 mg/day or both is inexpensive and presumably safe, and is likely to be cost-effective for preventing cardiovascular events if ongoing clinical trials confirm that homocysteine-lowering therapy is beneficial.<sup>32</sup>

Even without definitive evidence of clinical benefit, a case can be made for detecting and treating hyperhomocysteinemia in selected patients (ie, those with a history of premature cardiovascular disease, stroke, or venous thromboembolism, or those thought to be at high risk because other risk factors are present). In such cases, treatment is unlikely to cause harm and may produce an important benefit.

When starting homocysteine-lowering therapy, the goal should be to maintain the plasma concentration of total homocysteine within the laboratory's low-normal reference range. An American Heart Association science advisory statement suggested that a level of less than 10  $\mu\text{mol/L}$  is a reasonable target for patients at high cardiovascular risk.<sup>44</sup> A European expert panel has proposed a slightly higher target level (13-15  $\mu\text{mol/L}$ ).<sup>12</sup> Because excess folate intake may exacerbate neurological complications in people with occult pernicious anemia, vitamin B<sub>12</sub> status should be determined before starting folic acid therapy.

**Blood samples for homocysteine must be processed quickly**





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