Homocysteine - Test Overview

Introductory Statement
This edition of the PCS Newsletter presents information and research from a variety of sources on Homocysteine. Some basic information is included for those desiring a foundation and to familiarize our professional members with what many patients may have read or heard. Homocysteine has become a buzzword in health care because of its connection to cardiovascular disease, America’s #1 cause of death.

The basics of Homocysteine:
- Byproduct of protein metabolism
- Metabolized/detoxified in the liver
- Risk factor for cardiovascular disease
- Necessary nutrients include B-12, folate, B-6, di or trimethylglycine

Boston pathologist Kilmer McCully first proposed in 1968 that elevated levels of homocysteine were associated with cardiovascular disease. He is the author of The Homocysteine Revolution. As with many other pioneers in medicine, he was blacklisted for his brilliance.

From Medline Encyclopedia…
An amino acid (C₄H₉NO₂S) produced in animal metabolism by the demethylation of methionine to form a complex with serine that breaks up to then produce cysteine and homoserine.

Homocysteine is an amino acid in the blood. Too much of it is related to a higher risk of coronary heart disease, stroke and vascular disease (fatty deposits in peripheral arteries).

From Lab Corp’s Directory Of Services…
Ordering Code 706994  CPT Code 83090
Homocysteine:
- male: 6.3-15.0 µmol/L
- female: 4.6-12.4 µmol/L
- Comment – optimal levels are generally considered to be < 9 µmol/L with some calling for < 7 µmol/L.

Hyperhomocysteinemia can be categorized clinically as:
- moderate: upper limit of normal to 30 µmol/L
- intermediate: >30-100 µmol/L
- severe: >100 µmol/L

This test is intended for use in screening patients who may be at risk for heart disease and stroke. This test is not intended for use in the diagnosis of folate or vitamin B₁₂ deficiency.

Homocysteine can be considered to be an independent risk factor for the development of
cardiovascular disease.\textsuperscript{1,2,3} Patients with cardiovascular disease, including heart disease, stroke, peripheral vascular disease, and thromboembolic disease, generally have higher homocysteine levels than matched controls. The results of a large number of epidemiological studies have been analyzed through a meta-analysis.\textsuperscript{1} The increased risk, or odds ratio (OR), for coronary artery disease in patients with increased homocysteine levels was estimated to be 1.7. The OR for stroke was estimated to be 2.5 and the OR for peripheral vascular disease was estimated to be 6.8. Several conditions, other than specific genetic defects or cardiovascular disease, have been associated with hyperhomocysteinemia.\textsuperscript{1} These include vitamin deficiencies, advanced age, hypothyroidism, impaired kidney function, and systemic lupus erythematous. Medications including nicotinic acid, theophylline, methotrexate, and L-dopa have been reported to cause elevated homocysteine levels. 

References...


**Related Laboratory Tests**

**Primary:** Vitamin B-12 & Folate, Vitamin B-6, 
**Secondary:** Cholesterol, Triglycerides, Apolipoproteins, Lipoprotein (a), Fibrinogen, Creatine Kinase (CK), Calcium/Phosphorus Ratio, Monocytes, C-Reactive Protein HS, Cardiac Troponin and Insulin.

**Homocysteine Metabolism**

Reasons for elevation of homocysteine include:

- Genetic defects
- Excess methionine-rich food
- Inadequate intake of folic acid, vitamins B6 and B12, and methyl donors.

Homocysteine is a by-product of methionine metabolism. Methionine is particularly important because it supplies sulfur—a mineral—that helps to maintain healthy skin tone, well-conditioned hair, and strong nails. Methionine is thought to keep fat from building up in the liver. When certain enzymes do not completely transform the amino acid methionine, present in chicken, beef, tuna, shrimp, cheese and eggs, into derivatives needed for the formation of protein in tissues, there is a pathological buildup of homocysteine, an intermediate product. Although the chemistry is quite complicated involving many reactions, several are of critical importance.

The conversion of homocysteine back to methionine is called remethylation. B-12 catalyses the transfer of a methyl group to homocysteine. Methyl groups are needed for conversion of homocysteine to methionine, which also provides precursor material for SAMe. SAMe has been linked to emotional well-being and at least one study cited later in this newsletter supports the connection between elevated homocysteine and anger.

Homocysteine can be metabolized to cysteine through transsulfuration by two B-6 dependent enzymes – cystathionine b-synthase and cystathionase. Homocysteine can be converted back to methionine by folate dependent methionine synthase reaction or by methyltransferase reactions requiring methyl donors from the Trimethylglycine (Betaine) or dimethylglycine (DMG) molecule. Methyltransferase is a zinc metalloenzyme!

In some people, the enzymes required to facilitate transsulfuration or folate-based methylation are deficient, leading to homocysteine elevation despite adequate folate and/or vitamin B6 intake. Betaine has been shown to be quite effective in reducing high homocysteine levels in these cases. When levels of these critical nutrients (B-6, B-12, Folate and methyl groups) are low, normal metabolism cannot proceed efficiently, allowing homocysteine to accumulate. Because of its relationship to methyl and sulfur metabolism, Phase 2 detox may be affected in elevated homocysteine.

NOTE: animal protein contains about three times more methionine in than plant protein.

Comment: It should be noted that hyperhomocysteinemia was first noted in children and young adults with cardiovascular disease by Dr. McCully, so testing may be worthwhile in all age groups to eliminate this genetic defect and the effects of poor dietary habits in younger Americans from consideration and/or to establish need for nutritional intervention.

Research Information
From American Heart Association Literature
Two reports have strengthened the evidence for the relationship of homocysteine to stroke and cardiovascular disease:

- A large multi-center European trial found that men and women under 60 had a 2.2 times overall higher risk of cardiovascular disease if total homocysteine levels in their blood were in the top fifth of the normal range. This risk was independent of other risk factors but was notably higher in smokers and people with high blood pressure.
- A Norwegian study of 587 patients with coronary heart disease found that their risk of death after four to five years was proportional to total homocysteine levels in the blood. The risk rose from 3.8 percent in those with the lowest levels (below 9 micromol per liter) to 24.7 percent with the highest levels (greater than 15 micromol per liter).

Other evidence suggests that homocysteine may promote atherosclerosis by damaging the inner lining of arteries and promoting blood clots. However, a causal link hasn't been established.

Arterial stiffness related to homocysteine concentration.
Arterial stiffness in the central elastic arterial system increased rapidly at high plasma homocysteine concentrations. In 18 healthy middle-aged subjects, systemic arterial compliance (SAC) was measured over 5 hours after a standard methionine load. Arterial stiffness increased by 22% at 2.5hr and by 19% at 5th hour. 


Elevated homocysteine and hypertension = a double negative
A high plasma tHcy level is associated with history of hypertension and recurrent stroke among patients presenting with acute ischemic stroke. Hypertensive stroke patients with hyperhomocysteinemia should be identified as high-risk patients as compared to non-hypertensive stroke patients, and more vigorous measures for secondary prevention may be warranted.


Rheumatoid arthritis patients may be more susceptible to homocysteine elevation
The coincidence of higher homocysteine and lower folate concentrations with increased concentrations of immune activation markers in patients with RA suggests that immune activation could be involved in the development of hyperhomocysteinaemia.


Hyperhomocysteinemia as a component of Syndrome X.
Two groups of rats were fed either fructose-enriched diet or standard rat chow for 5 weeks. Systolic blood pressure (SBP), as well as fasting plasma insulin, triglycerides, total cholesterol, and total homocysteine levels, were determined at the beginning and at the end of the study. A complete metabolic syndrome was induced by the fructose-enriched diet, including hyperinsulinemia, hypertriglyceridemia, and hypertension. Homocysteine concentration was 72% higher after 5 weeks on the fructose diet. Insulin, triglycerides, SBP, and homocysteine levels were insignificantly changed during 5 weeks on standard rat chow. It is thus highly likely that hyperhomocysteinemia is an integral component of the human syndrome X as well.

Comment: Since the reference range for glucose is being lowered to 100, the percentage of Americans with Syndrome X will increase substantially from the 25% estimated by a JAMA article (JAMA 2002, Jan. 16; 287(3):356-9). 33% of Latin Americans were estimated to have Syndrome X in the same article. It is of interest to note that insulin levels were not considered in JAMA.

Mild elevations in homocysteine associated with arterial calcification.
Aortic calcification was demonstrated in vascular smooth muscle cells in experimental animal models of mild hyperhomocysteinemia. Life Sci. 2003 Dec 12;74(4):451-61

Comment: the concept of free calcium excess becomes even more important in this situation. The optimal balance between calcium and phosphorus is considered to be 2.5:1, based on the work of Dr. Melvin Page circa 1950.

Hostility, anger linked to chemical that may cause heart disease.
Men who reported that they consistently held in angry feelings also showed higher levels of homocysteine.
"We know from our work and that of others that people who are hostile have a chronically "turned-on" sympathetic nervous system," she said. "They have higher blood pressure, higher heart rates and higher cholesterol among other things."
"One potential picture emerging from the current data is that men, particularly high-hostile men, have a sympathetic nervous system that is always turned on, resulting in higher homocysteine levels."
Life Sciences April 28, 2000

Plasma Homocysteine as a Risk Factor for Dementia and Alzheimer’s Disease
1092 subjects without dementia (667 women and 425 men; mean age, 76 years) from the Framingham Study constituted our study sample. An increased plasma homocysteine level is a strong, independent risk factor for the development of dementia and Alzheimer’s disease. NEJM Volume 346:476-483, February 14, 2002 Number 7

Levels of homocysteine related to risk of CAD

<table>
<thead>
<tr>
<th>Homocysteine (µmol/L)</th>
<th>Mortality (%)</th>
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<tbody>
<tr>
<td>&lt;9</td>
<td>3.8</td>
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<tr>
<td>9-14.9</td>
<td>8.6</td>
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<tr>
<td>≥15</td>
<td>24.7</td>
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Copper and Homocysteine

Comment: this article only looks at copper, but it seems possible that heavy metals in general will be linked to aggravation of the neurodegenerative process.

Nutritional Considerations
Comment: It is noteworthy that the universally accepted therapy for elevated homocysteine involves only nutritional intervention without the use of drugs.

Reduction of Homocysteine with B Vitamins.
Reduction of plasma homocysteine was noted in apparently healthy elderly subjects after treatment with folic acid, vitamin B12 and vitamin B6. Four months of oral daily supplementation with 0.5 mg cyanocobalamin, 0.8 mg folic acid and 3 mg vitamin B(6). There was a significant decrease in P-tHcys (plasma homocysteine) after 4 months of vitamin treatment. CONCLUSIONS: Sub optimal vitamin status is an important cause of elevated P-tHcys and S-MMA in apparently healthy elderly subjects. Oral B-vitamin therapy is an effective and convenient way to normalize P-tHcys and S-MMA. Eur J Clin Nutr. 2003 Nov;57(11):1426-36.

Red Wine Prevents Homocysteine-induced Endothelial Dysfunction.
The effect of red wine on homocysteine-induced endothelial dysfunction in porcine coronary arteries was studied in this well controlled situation. Coronary artery rings treated with homocysteine (50 muM) showed a significant
reduction of endothelium-dependent vasorelaxation by 43%, while rings treated with red wine plus homocysteine showed no significant difference. Homocysteine significantly impaired endothelial functions and red wine effectively prevented homocysteine-induced this dysfunction. This study suggests that protecting coronary endothelial cells from homocysteine damage may be an important mechanism of red wine for preventing coronary artery disease. J Surg Res. 2003 Nov;115(1):82-91.

Vitamin C Shown to Protect Arteries Against Homocysteine,

When individuals in the study ingested methionine then took a megadose (2 grams) of vitamin C, their large and small blood vessel function rapidly improved.

Homocysteine damages blood vessel linings by increasing the number of oxygen free radicals. High cholesterol can cause risk factors for heart attacks through the same mechanism "At this time we do not suggest using megadoses of vitamin C to reverse the risk of high homocysteine levels," he said. "However, the findings indicate that if vitamin B treatments do not lower homocysteine levels, then antioxidants might work to help protect blood vessels and prevent heart attack and stroke." Circulation Sept. 14, 1999

Comment: An unbalanced high protein diet will also lead to acid stress, making the environment for free radicals even more dangerous. Use of pH paper to monitor acid/base balance is of great benefit.

Excerpts from an overview article in Circulation

Meta-analysis of 12 clinical studies estimates that a 25% reduction in homocysteine concentration can be achieved with mean supplementation of 0.5 to 5.7 mg of folic acid per day; an additional 7% lowering has been observed after the addition of vitamin B₁₂ (0.02 to 1 mg/d; mean, 0.5 mg).

Food and Nutrition Board of the Institute of Medicine has recommended an upper limit of 1 mg/d folic acid on the basis of the possibility that higher doses may mask signs of vitamin B₁₂ deficiency in some subjects. In overt cobalamin deficiency with intermediate and severe hyperhomocyst(e)inemia, vitamin B₁₂ can normalize homocysteine concentration in 70% of cases.

50 mg of vitamin B₆ per day independently reduced the post–methionine-loading increase in homocyst(e)ine levels by 22%.

In a placebo-controlled study, a combination of multiple agents including folic acid (0.65 mg/d), vitamin-B₆ (10 mg/d), and vitamin B₁₂ (0.4 mg/d) was very effective in reducing homocysteine levels in patients with moderate or intermediate hyperhomocysteinemia.

Of note, the relationship between vitamin B₆ and vascular disease was shown to be independent of homocysteine levels.

Vitamin intake from food sources (1 mg of folic acid, 12.2 mg of pyridoxine, and 50 µg of cyanocobalamin per day) failed to maintain normal homocysteine levels attained previously by vitamin supplementation.

Pharmacological doses of nicotinic acid (3000 mg/d) may cause significant elevations. Daily food intake of 0.6 mg of riboflavin, a vitamin that can function as a cofactor for MTHFR (methylene-tetrahydrofolate reductase) results in modest reductions in homocyst(e)ine (0.475 µmol/L).

Users of multivitamin supplements in observational studies have lower homocysteine levels than nonusers.

Daily food intake of 0.6 mg of riboflavin, a vitamin that can function as a cofactor for MTHFR, results in modest reductions in homocyst(e)ine (0.475 µmol/L) Circulation. 1999;99:178-182

Comments: unfortunately, this article consistently lists "fortified" cereal products as sources for vitamins to resolve homocysteine issues. We hope the editors of Circulation take note of the recent article in Metabolism, reviewed above, concerning Syndrome X and homocysteine. A balanced B complex should be given with high doses of any single B. The elderly may have increased risk of B-12 deficiency related to lack of intrinsic factor for absorption.
TMG reduces homocysteine
Betaine supplementation has been shown to reduce homocysteine levels. *Metabolism* 1985;12:1115-1121

Betaine-dependent homocysteine re-methylation and the subsequent decrease in plasma homocysteine can be maintained as long as supplemental betaine is taken.

www.pdrhealth.com

NOTE: average dose recommendation is ~ 250 mg. Per day. Some sources recommend up to 1200 mg.

In the sixties DMG was marketed as part of B-15/pangamic acid. The supplement was highly regarded as an athletic performance enhancer!

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**Next Topic: Fibrinogen**

Your comments and suggestions are welcome and may be included in future newsletters.

**Thank you!**

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FDA has not commented on the above-mentioned studies or statements

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