

Homocysteine

What is it?
What does it do?

The Compelling Case for Homocysteine Assay

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The homocysteine assay is a significant, essential part of preventive health care. Research and statistics show that analysis of a patient's homocysteine level provides an immediate, important and integral tool in determining treatments and care. The complexity and severity of the many diseases affected by elevated homocysteine levels demand that this simple test be a standard part of every adult's physical examination.

During the past thirty-five years epidemiological studies have unequivocally established that an elevated plasma homocysteine level- denoted hyperhomocysteinemia- both predicts and precedes the occurrence of cardiovascular disease, stroke, and thromboembolic disease. This hypothesis also meets the established criteria of causality, such as consistency, strength, temporality, and biological plausibility.

Homocysteine is a toxic, non-protein, sulfur containing amino acid in humans. It is formed exclusively upon demethylation of methionine, an essential amino acid. Homocysteine is metabolized either through remethylation or transsulfuration pathways and is nutritionally regulated.

Hyperhomocysteinemia can result from deficiencies of vitamin cofactors (B₆, B₁₂, folic acid) required for homocysteine metabolism and/or from genetic disorders of its metabolism. The C677T methylene tetrahydrofolate reductase (MTHFR) gene mutation found in up to 15% of the population is a known cause for elevated homocysteine levels in plasma. Mutations in cystathionine beta-synthase (F1278T) and methionine synthase (A2756G) genes also cause hyperhomocysteinemia. The newly described 1298 A-C mutation in the MTHFR gene clearly reduces MTHFR activity and produces elevated plasma homocysteine levels. The newly discovered cystathioninuria 1364 T/T gene homozygotes have significantly higher mean plasma homocysteine concentrations than subjects with other genotypes.

Hyperhomocysteinemia results from an imbalance between the influx of homocysteine into the circulation and the clearance of homocysteine from the plasma. Hyperhomocysteinemia results in progressive atherogenesis in the arteries of the limbs, the coronary arteries, and the cerebrovascular system. **Hyperhomocysteinemia offers an explanation for human atherosclerotic disease that is difficult to explain by the cholesterol/fat approach, a concept that is in opposition to the official party line of heart establishment authorities. The National Library of Medicine (Pub Med) contains 9,266 citations for homocysteine in its database.**

There is overwhelming experimental evidence that confirms the pathophysiological mechanisms of hyperhomocysteinemia that causes multiple disease states. Homocysteine unleashes a veritable storm of inflammation mediators. The sulfhydryl group of homocysteine undergoes auto-oxidation, generating superoxide radicals, which consume the vasodilator NO to form peroxynitrite. Hyperhomocysteinemia induces vascular smooth muscle proliferation. **Homocysteine induces endoplasmic reticulum stress, leading to activation of the unfolded protein response. This is followed by programmed cell death of human vascular endothelial cells.** Cell death by homocysteine is specific. Homocysteine produces endothelial dysfunction, inflammation and injury. This is followed by platelet activation and thrombus formation.

Homocysteine influences multiple blood clotting factors. The endothelial surface plays an important role in the pathogenesis of atherosclerosis and the regulation of coagulation. Perturbed endothelial cells generate pro-coagulant activity - while under normal conditions, they possess multiple antithrombotic and anticoagulant mechanisms. Homocysteine inhibits the expression and activity of endothelial cell surface

thrombomodulin, the thrombin co-factor responsible for Protein C-- activation. The protein C enzyme system appears to be one of the most important anticoagulant pathways in the blood. Protein C deficiency leads to arterial or venous thrombosis with the subsequent development of atherosclerosis. Elevated plasma homocysteine leads to the modification of fibrinogen, resulting in altered fibrin clot structure. These clots that are abnormally resistant to fibrinolysis may explain in part the increased risk of thrombosis in hyperhomocysteinemia. Homocysteine also inhibits antithrombin III binding activity of endothelial heparin sulfate proteoglycan thereby suppressing the anticoagulant effect of antithrombin III. Homocysteine interferes with the fibrinolytic properties of the endothelial surface because it inhibits the bindings of tissue plasminogen activator. Homocysteine increases thromboxane formation. Homocysteine suppresses heparin sulfate expression - a normal anticoagulant. Homocysteine breaks up proteoglycans, damaging the integrity of the vessel wall.

Homocysteine may exert its atherogenic effect in part through chemokine mediated mechanisms. Chemokines are potent chemo-attractant cytokines that are produced locally in tissues and direct the migration and homing of leukocytes. Monocyte chemo-attractant protein 1 is a potent chemokine that stimulates the migration of monocytes into the arterial wall. Homocysteine increases monocyte adhesion and transmigration eventually bringing about endothelial damage through the release of H_2O_2 . Monocytes also absorb modified low-density lipoproteins that are modified by homocysteine. One of the earliest events in the formation of atherosclerotic plaque is the adherence of circulating monocytes to the vascular endothelium through which they gain entry to the sub-intimal tissue and are transformed into lipid-laden foam cells

Homocysteine decreases endothelial NO availability by generating nitrotyrosine. Decreased NO availability is associated with increased matrix metallo-proteinase (MMP) activity. MMPs, also called matrixins, are a family of 23 enzymes that play a vital role in all stages of the wound healing process. Over expression of MMPs results in excessive extra cellular matrix degradation leading to tissue destruction. The accumulation of oxidized matrix between the endothelium and myocytes is associated with endocardial endothelial dysfunction and heart failure. The activation of MMPs leads to decreased cardiac tissue tensile strength and may cause systolic and diastolic dysfunction and loss of cardiac function. Homocysteine exerts its atherogenic effect in part by elevating levels and activity of MMPs, which in turn may enhance matrix degradation. Increased MMP activity has been demonstrated during atherosclerotic lesion progression and plaque disruption. This leads to the clinical symptoms of atherosclerosis, unstable angina, myocardial infarction and stroke.

Hyperhomocysteinemia interferes with the vasomotor dilatation, and vasoconstriction follows. **Hyperhomocysteinemia directly damages the vascular matrix.** Hyperhomocysteinemia induces the metabolic accumulation of S-Adenosyl-L Homocysteine which in turn inhibits the metabolic breakdown of catecholamines. This results in elevation of blood and tissue catecholamine levels that over-stimulate the cardiovascular systems and functions. As a result of the constant exposure to high levels of endogenous catecholamines, vascular cells incur chronic cumulative damage, and hypertension follows. Homocysteine inhibits endothelial cell proliferation, which plays a key role in angiogenesis. Angiogenesis is necessary for the development of collateral circulation in patients with coronary artery disease. **Homocysteine induces endocardial cell**

(capillary) apoptosis and reduces the capillary cell density. This leads to heart failure.

Homocysteine is a neurotoxic amino acid that potentiates endothelial and neuronal oxidative injury in Alzheimer's disease and vascular dementia. Homocysteine also potentiates both amyloid-beta and glutamate neurotoxicity. Homocysteine induces cell death of astrocytes. Hyperhomocysteinemia impairs memory, an effect mediated by oxidative stress. Homocysteine may damage the hippocampus. Elevated levels of homocysteine may be associated with brain atrophy in healthy elderly subjects. Chronic alcoholics also have elevated homocysteine and brain atrophy levels. Psychogeriatric patients have elevated homocysteine levels. Hyperhomocysteinemia is associated with decreased cognitive performance in non-demented elderly people.

Homocysteine inhibits the hydrolysis of S-adenosyl homocysteine leading to a decrease in intracellular adenosine concentration. Adenosine is generated during the metabolism of homocysteine. Adenosine dilates coronary and cerebral arteries, inhibits platelet aggregation, and decreases proliferation or growth of smooth muscle cells. Adenosine prevents the adhesion of neutrophils to the endothelium and increases blood flow in the microcirculation. Adenosine inhibits the generation of superoxide anions. **Hyperhomocysteinemia significantly decreases plasma and tissue adenosine levels.** This decrease in plasma and tissue adenosine may be an important mechanism mediating the pathogenic effects of hyperhomocysteinemia. Reduced adenosine levels in plasma or tissue results in dysfunction of the heart, blood vessels and the kidneys thereby increasing the risk of cardiovascular disease, kidney disease, Alzheimer's disease and other diseases.

Many individuals who consume large amounts of food rich in animal protein may ingest two to three grams of methionine resulting in postprandial homocysteine concentrations greater than 20 micromoles/L. **Moderate hyperhomocysteinemia, 20 micromoles/L, impairs endothelial dependent vasodilatation by decreasing bioavailable nitric oxide.** Nitric oxide plays many important roles that are relevant to the pathogenesis and the pathophysiology of atherosclerosis. Nitric oxide inhibits the adhesion, activation, and aggregation of platelets. Nitric oxide reduces the adhesion and emigration of leukocytes into the vessel wall and limits the growth of vascular smooth muscle cells. Meals high in animal protein may lead to repeat episodes of endothelial dysfunction, which may in turn predispose the individual to atherosclerosis and hypertension.

Hyperhomocysteinemia is a risk factor for cancer and a new potential tumor marker. Hyperhomocysteinemia causes aberrant DNA methylation. Hyperhomocysteinemia is a biomarker of disruption of one-carbon metabolism. DNA damage may be caused by the over-production of oxygen free radicals generated from oxidation of homocysteine. Oxidation of DNA may cause gene mutations, such as P53 and ras genes, and eventually lead to carcinogenesis.

Hyperhomocysteinemia is a risk factor in women suffering from habitual abortions, placental abruption, placental infarcts, pre-eclampsia, intrauterine growth retardation and low birth weight. **Homocysteine causes pregnancy complications related to trophoblast death and the inhibition of trophoblast gonadotropin secretion.** Hyperhomocysteinemia is also implicated in Parkinson's disease, cleft palate, retinal vein occlusion, diabetic retinopathy, schizophrenia, depressive disorders, Raynaud's syndrome, Alzheimer's disease, and lupus erythematosus, glaucoma, cerebral

vein thrombosis, osteoporosis, Down's syndrome, liver steatosis, immune dysfunction and sudden sensorineural hearing loss. Hyperhomocysteinemia is an independent and modifiable risk factor for ischemic vascular disease, thrombophilia, fibrotic heart disease, dementia, defects of the heart and neural-tube, hypertension, chronic renal failure, recurrent stroke, Crohn's disease, insulin resistant diabetes, colon cancer, breast cancer, invasive cervical cancer and venous thrombosis.

Plasma homocysteine predicts mortality independently of traditional risk factors and C-reactive protein in patients with angiographically defined coronary artery disease. Elevated homocysteine levels are a modifiable risk factor for restenosis after coronary angioplasty. Homocysteine-lowering therapy significantly decreases restenosis rates after percutaneous coronary intervention. Plasma homocysteine levels are significantly higher in patients with unstable angina. Hyperhomocysteinemia causes carotid artery intima-media thickness, which is an early sign of atherosclerosis. Hyperhomocysteinemia is a predisposing condition for spontaneous cervical dissection as well as the progression of aortic atherosclerosis. Hyperhomocysteinemia may be an important factor in primary pulmonary hypertension. Hyperhomocysteinemia is a risk factor for heart transplant graft failure. Hyperhomocysteinemia is a risk factor for the development of congestive heart failure without prior myocardial infarction and increases the risk of recurrent stroke. Smoking-induced homocysteine elevations may raise systolic blood pressure. Hyperhomocysteinemia increases saphenous vein occlusion after coronary artery bypass and increases the risk of restenosis after carotid endarterectomy.

Cardiovascular disease, including stroke, is the leading cause of

illness and death in the USA, accounting for over 50% of all deaths. **Plasma homocysteine is a strong predictor of both cardiovascular and non-cardiovascular mortality.** Hyperhomocysteinemia is preventable and reversible. Homocysteine intervention strategies include B vitamins (B₆, B₁₂, and folic acid), betaine, cessation of smoking, increased physical activity, and reduction of alcohol intake. The use of polyvitamin therapy to lower homocysteine levels is inexpensive and well tolerated.

Homocysteine levels greater than nine micromoles/L place a person at greater risk for stroke, heart disease, and non-cardiovascular death. Merely prescribing folate for everyone can be a lethal misconception. Women over forty, because of gastric atrophy absorb B₁₂ at a lesser rate. Multivitamin preparation containing folic acid may not dissolve quickly enough to release their contents in the critical folate absorption area (first third of the jejunum). The disintegration time of commercially available multivitamin supplements is highly variable. Impaired product performance such as failure to disintegrate and/or dissolve in the gastro-intestinal tract could limit the absorption of vitamins. The presence of vitamin C may deplete the available contents of B₁₂ and folic acid when the mixture remains in the stomach.

There are multiple disease states (sickle-cell anemia and hypothyroidism) that elevate homocysteine levels. Psychological stress is associated with elevated homocysteine levels. Increased plasma homocysteine concentrations are found in healthy people with hostile behavior. **Many commonly prescribed medications, including certain cholesterol lowering medications, Methotrexate, Levodopa, Niacin, Diuril, anabolic steroids, anti-seizure medications, Metformin, Cyclosporin, Trimethoprim, histamine-receptor antagonists and**

proton-pump inhibitors elevate plasma homocysteine levels. Total plasma homocysteine increases throughout life. Decreasing levels of melatonin during aging may lead to hyperhomocysteinemia. Approximately 5-15% of the elderly are deficient in vitamin B₁₂. Organic acids in selected foods, as well as alcohol and smoking, reduce the bioavailability of dietary folate. Vitamin bioavailability may be compromised from certain vegetables (particularly raw) and/or from high-fiber foods, because of limited digestion and inefficient release of vitamins from the food matrix.

At the present time there are multiple clinical studies in progress to establish whether homocysteine is the “culprit” or merely an indicator of something else that does the damage. There is overwhelming evidence to support it being the “culprit.” The current large randomized ongoing homocysteine lowering studies are fundamentally flawed, since participants continue to ingest fortified flour that contains folate, B₆, and B₁₂ in their diets. Many of these same participants have also changed their lifestyles by restricting their use of nicotine, caffeine, and alcohol. **If the physician postpones having his patient’s homocysteine level assayed, awaiting the final results of the various clinical studies which will be available in two to five years, his patients may not be around to hear the final verdict.**

Among available determinants of folate/cobalamine levels, the homocysteine assay is a swift and sensitive marker. The physician needs to analyze the patient’s homocysteine level, then titrate the dose of folic acid and cobalamine to bring the blood levels of homocysteine below nine micromoles/L. **Measuring blood levels of homocysteine is a “potential lifesaving test.”**

Physicians often decide not to order a homocysteine assay for their patients, citing the cost of the homocysteine assay, equivalent to the cost of

one carton of cigarettes, two pounds of Fannie May[®] chocolates, or two OpusX[®] cigars. These same physicians state, “It is not cost effective.” Maybe the patients who have entrusted their care as well as their lives with these physicians should ask what is the emotional, economic and social cost of a heart attack, stroke, loss of a pregnancy, having a still-born infant, chronic dialysis, a hysterectomy for cancer, surgery for cancer of the colon, the treatment of breast cancer, having a child born with a neural tube defect, or a child born with congenital heart defect, living with someone with mental illness, or providing custodial care for a loved one with Alzheimer’s or Parkinson’s disease? **Rather than adding “test less” to the prevailing “treat more” ethos, perhaps “test more, treat more selectively” represents more appropriate medical care.**

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Specific references can be furnished upon request.

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