The Role of Homocysteine in Human Health

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Introduction

For the last two decades, the Modus Operandi of most health care providers managing their patients with atherosclerosis was to prescribe cholesterol-lowering drugs. It would seem that this essential sterol has been inadvertently implicated for the epidemic of atherosclerotic and thromboembolic disease, which has permeated our society and over-burdened our health care system.

The most popular pharmaceutical management tool has been the statin class of cholesterol-lowering drugs. These drugs are HMG-CoA Reductase inhibitors and function to interfere with cholesterol syntheses in the liver.[1] These drugs are widely prescribed to treat heart disease with the underlying presumption being that cholesterol is the definitive cause of coronary artery stenosis. Despite their questionable safety and the fact they deplete the myocardium of coenzyme Q10 (potentially increasing the risk of cardiac mortality), they continue to be one of the most frequently prescribed drugs. As the body of evidence regarding this controversial subject in cardiac management has continued to expand, clinicians are considering other factors, which may be more important with regard to prevention and management of cardiovascular disease. Some of these concepts relate to the inappropriate intake or metabolism of fatty acids, endogenous or exogenous lipid peroxidation, lipid or triglyceride reactivity to dietary stimuli, unchallenged free radical activity and various nutrient deficiencies. The most frequently cited of which include, vitamin C, vitamin E, coenzyme Q_{10}, magnesium, carotenoids, selenium, L-carnitine, Flavanoids, zinc and B-nutrients. Sub-clinical deficiencies of these nutrients are more prevalent than previously realized and they all subsequently play an important role in human health in many different ways.

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Importance of Homocysteine

In recent years, another important element in the genesis of atherosclerotic vascular disease has become manifest; that being elevated serum levels of homocysteine. The role of homocysteine as a causative factor in the development of vascular pathology was proposed by Dr. Kilmer McCully in 1969.[2] Homocysteinuria, the rare, autosomal-recessive disease frequently associated to advanced occlusive arterial disease, elevated plasma homocysteine levels and premature death from advanced cardiovascular disease, was used to link elevated homocysteine levels to vascular pathology.[3] This disease was known to be caused by an inherent lack of enzymic activity in the liver (cystathione synthetase), which is required to metabolize homocysteine into less harmful metabolites.[4] Certainly, homocysteine is receiving a great deal of research attention. As of January 2000, over 200,000 people are involved in 15 clinical trials investigating various aspects of homocysteine metabolism including the effects of nutrient supplementation upon test subjects.

Homocysteine is a sulphur-containing amino acid and a direct metabolic by-product of methionine metabolism. Homocysteine is typically measured as serum total homocysteine. However, this measurement also accounts for the oxidized components, homocysteine and cysteine–homocysteine. Total protein or methionine intakes may not correlate to blood levels of homocysteine. However, a single dose of methionine (100 mg/kg body weight) has been shown to elevate homocysteine levels and is frequently utilized to assess homocysteine metabolism.[5] Normal fasting

plasma homocysteine levels are considered to be between 5 and 15 μM/L. Hyperhomocysteinemia is considered when the concentrations of homocysteine are above 15 μM/L.[6]

There are several key nutrients, which function as co-factors in the metabolism of methionine and homocysteine. Folic acid and cyanocobalamin directly affect the activity of the enzymes methylemetetrahydrofolate, reductase and methionine synthase. Pyridoxine is a co-factor for cystathione-B-Synthase. These metabolic pathways control the accumulation of homocysteine, which has a deleterious effect upon vascular endothelial cells. Errors in this enzymic cascade may be due to a mutated gene which has been identified by Dr. Rima Rosen of McGill University but, more commonly, errors in homocysteine metabolism are closely linked to deficiencies in specific nutrients, particularly B_6, B_{12} and folic acid.[2] Like cholesterol, homocysteine is necessary to the human organism; if the appropriate co-factors are present it will convert to cysteine, ATP and S-adenosylmethionine.

Some speculation has arisen regarding limiting the intake of protein foods high in methionine. Not only is this idea inappropriate because of the importance of methionine in protein or amino acid metabolism (cartilage, carnitine, taurine), but this solution does not address the underlying problem of excessive homocysteine accumulation, which is attributable to deficiencies in key nutrients, necessary for its enzymic conversion. The relationship between homocysteine and B-vitamins is quite close. In fact, it has been suggested that homocysteine levels could reliably be used as a physiological marker to evaluate nutrient status.[2] This relationship and how it relates to cardiovascular disease is also very revealing. The use of synthetic hormones, smoking and alcohol deplete tissue stores of B_6, B_{12} and folic acid. It would subsequently, not be surprising that these groups would have higher levels of homocysteine and a concurrent increased incidence of heart disease. Elevated levels of homocysteine have been identified in 21% of patients with coronary artery disease, 24% of patients with cerebrovascular disease and 32% of patients with peripheral vascular pathology. Some researchers have indicated that homocysteine levels are up to 40 times more predictive than total Serum cholesterol in assessing cardiovascular disease risk.[2]

Homocysteine is thought to be one of the early factors predisposing one to the development of the atherosclerotic lesion by injuring vascular endothelium.[7] Typical studies have indicated that patients with arterial occlusive disease and hyperhomocysteinemia show elevated levels of endothelium-derived proteins such as, thrombomodulin, VonWillebrand Factor and tissue-type plasminogen activator.[7] These proteins are secreted by damaged endothelial cells resulting from constant free-radical exposure produced by homocysteine. Many of these studies have used various B-vitamins to lower homocysteine and endothelium-derived proteins.[7] Other studies have directly linked low levels of B-nutrients to homocysteinemia and low levels of tissue folate to increased coronary artery risk.[8] Other reports have linked elevated homocysteine levels with an increased, independent risk of atherogenesis and thromboembolism.[9,10] Studies have linked homocysteine with the promotion of lipid peroxidation, interference with platelet aggregation, and fibrin metabolism.[11] Certainly, circulating plasma lipids play an important role in the development of atherosclerotic lesions. Oxidation of intra or extracellular endothelial LDL lipids is known to be one of the earliest lesions that develops in endothelial tissue.[17] It has also been postulated that homocysteine enhances LP(A) adherence to fibrin, an inherent mechanism by which damaged endothelium tries to repair itself.[12]

Endothelial tissue continuously secretes nitric oxide, which relaxes the smooth muscle cells that line the tunica media. Damaged endothelial cells can also secrete vasoconstrictor factors, (endothelin-1) and factors which affect the growth of smooth muscle cells, vascular permeability and vascular adhesive capability.[13] Other reports indicate that hyperhomocysteinemia is associated with impaired endothelium-dependent vasodilation in humans.[14] Some other studies have shown vascular-wall damage caused from high homocysteine levels attributable to increased endothelial levels of thiolactone and low levels of oxidase.[15,16] These factors are associated with higher levels of oxidative stress within endothelial tissue. There are other theories pertaining to the mechanism by which homocysteine inflicts chemical harm upon vascular structures. Another plausible explanation may involve the enhanced secretion of cholesterol and Apo-B from hepatocytes following elevated levels of homocysteine.[23] Chronic, elevated levels of homocysteine also have an impact upon cellular methylation reactions involving DNA, RNA, various proteins and phospholipids. Excessive levels of homocysteine negates the enzyme S-adeno-sylhomocysteine hydrolase which causes excessive binding of S-adenosylhomo-cysteine to active cellular methyltransferase sites.[18]

Regulating Homocysteine

There exists a multitude of evidence to indicate that high levels of homocysteine is a major risk factor in the development of vascular pathology.[19-23] There is also a great deal of evidence to suggest that the addition of vitamins B_6 (100 mg), B_{12} (1 mg), and folate (5-15 mg) to the diet in a supplement form can normalize high levels of circulating homocysteine. Studies indicate that test subjects are frequently deficient in the essential nutrients that regulate homocysteine metabolism.[24-29] Using supplements such as B-vitamins (Folate, B_{12}, B_6) and trimethylglycine which remethylates homocysteine into methionine and S-adenosylmethionine is clinically prudent. Choline and zinc are also required to remethylate homocysteine and should also be considered.[30-34]

Plasma concentrations of homocysteine increase with age, male gender, impaired renal function, nutrient deficiency and genetic factors. The odds ratio for ischemic heart disease has been estimated to be 1.4 for every (.5 μmol/L) increase in total plasma homocysteine.[35] That confers a 6-7% increase in risk for having a stroke or myocardial infarction for every 1 μmol/L increase in total homocysteine.[36] With an increase in each tertile intake of folate, B_6 and B_{12} a concomitant decrease in homocysteine of .4–.7 μmol/L is produced.[37] This chemical relationship has caused an interest in increasing vitamin fortification of our current food supply, more specifically with folic acid.[38]

There have been several large studies indicating that elevated homocysteine levels can lead to vascular disease. A large, European trial, published in the June 1997 *Journal of the American Medical Association* indicated that adults had 2.2 times higher risk of developing vascular disease if their plasma homocysteine levels were in the top fifth of the normal range compared with those in the bottom four-fifths. This risk was independent of other risk factors but was higher in smokers and those with hypertension. A Norwegian study, which appeared in the July, 1997, *New England Journal of Medicine* indicated that the risk of death in patients with coronary artery disease was proportional to plasma total homocysteine levels. The risk rose from 3.8% in those with the lowest levels (below 9 μmol/L) to 24.7% with the highest levels (above 15 μmol/L). These studies and many more like them indicate the need for regular testing for homocysteine

levels so that appropriate risk factors can be properly assessed. Total plasma homocysteine status may also be used as a sensitive tool to assess red blood cell folate status.[35]

Professor Rene Malinow, from the Oregon Regional Primate Research Center, has stated in his study published in the *New England Journal of Medicine* that folic acid intake (between .2-5 mg per day) may be necessary to lower homocysteine levels and prevent an estimated 50,000 heart attacks per year in the United States. Dr. Malinow indicated that levels of vitamin fortification need to be at levels higher than the current government recommendation. FDA guidelines for nutrient quantity were found to be insufficient at lowering homocysteine levels. A level of at least 400 mcg. of folic acid per day is considered the minimum dose required.

It has been estimated that a 25% reduction in homocysteine can be achieved with mean supplementation of .5-5.7 mg of folic acid, and an additional 7% reduction has been observed after the addition of B_{12} (.02-1 mg/day, mean .5 mg).[36] Other studies have shown that vitamin B_6 can reduce homocysteine levels following a methionine load by 25%, and 22% utilizing dosages of 50-250 mg/day.[37-42] A combination of nutrients including folic acid, pyridoxine and B_{12} was very effective at reducing homocysteine levels in patients with moderate or intermediate hyperhomocysteinemia.[43] However, increasing vitamin intake from food sources (1 mg folic acid, 12.2 mg B_6, and 50 micrograms of B_{12} per day) did not maintain normalized homocysteine levels previously attained by supplements.[44] The daily use of fortified cereals containing 499 and 650 mcg of folic acid per serving and the RDA of other vitamins reduced homocysteine by 11% and 14% respectively.[45] Observational studies have indicated that the users of multivitamin supplements have lower homocysteine levels and also have higher concentrations of plasma folic acid, B_6 and B_{12} than non-users.[46]

The relationship between homocysteine and protein intake is rather obscure. A University of Iowa study indicated that high levels of protein in the diet can elevate homocysteine levels by increasing the methionine load. W. Haynes, M.D., indicated that increasing levels of methionine accompanied by a diet low in folic acid may cause blood vessel dysfunction. Haynes also stated the effect of vitamin C on large and small vessel function following methionine load. The addition of 2000 mg of Vitamin C rapidly improved large and small vessel function. Other reports have not supported this relationship between protein consumption and homocysteine levels.[47]

There are various methods by which homocysteine levels are controlled within the body. The most common pathway is the remethylation process by which methyl groups (CH_3) are donated to homocysteine to ultimately produce methionine and S-adenosylmethionine. This can be accomplished by using trimethylglycine (Betaine) at 500–9000 mg per day, B_{12} at 1000–3000 mcg per day, folic acid at 800–5000 mcg per day and zinc at 30–90 mg per day. Choline is also considered a methyl donor, but it does not require the other nutrients to methylate homocysteine. Choline only functions as a methyl donor in the liver and kidneys, not in other organs such as the brain and heart.[48]

The other pathway involves trans-sulfuration of homocysteine into cysteine and glutathione. This pathway is dependent upon adequate levels of vitamin B_6. The subsequent levels of vitamin necessary to control homocysteine are dependent upon other nutrient levels (folate and B_{12}) and methionine intake. Supplementation with 100–600 mg of B_6 per day is usually adequate. Those requiring greater amounts may have a genetic deficiency in the cystathione–B synthase enzyme which regulates the trans-sulfuration pathway.[48] At the University of Michigan, R. Matthews

discovered how folates lower high homocysteine levels. His findings indicated that folic acid assists the binding of flavin adeninedinucleotide (FAD) to the enzyme methylemetetrahydrofolate reductase. This enzyme is essential in catalyzing the conversion of homocysteine to methionine. Trimethylglycine is thought to stimulate activity of the enzyme betaine: homocysteine methyltransferase in the liver.[49]

The risk of stroke or heart attack is increased following mild elevations in homocysteine. It appears that there is no "safe" normal range of homocysteine concentration. Studies indicate that homocysteine levels above 6.3 μmol/L cause a steep, progressive increased risk of heart attack. A study published in the *American Journal of Epidemidogy* indicated that each 3-unit increase in homocysteine equates to a 35% increase in risk of myocardial infarction.[49] A recent study published in *Cardiologica* indicated that the average American's homocysteine level is 10 mg μmol/L. It appears a safer range one would want to achieve would be below 6.3 μmol/L of blood.[49] Scientists like R. Macko of the Baltimore Veterans Administration Medical Center has indicated the research illustrates that there is a clear risk associated to even small increases in homocysteine levels. Macko found that lowering homocysteine levels with B vitamins decreased levels of markers indicative of vessel-wall damage (thrombomodulin) and decreased the risk of stroke and heart attack. A study published in the August 1999 issue of *Stroke* indicated that younger women who had the highest levels of homocysteine had double the increase in risk of stroke compared to women with lower levels. Dr. S. Kittner, who headed the study indicated that the potential to improve public health and reduce the risk of stroke and other forms of cardiovascular disease by using nutritional intervention is significant. It should also be mentioned that elevated homocysteine levels have been closely linked to altered DNA repair, Alzheimer's Disease, Chronic Fatigue Syndrome and Rheumatoid Arthritis.[48-49]

In the January 1999 issue of *Circulation,* the American Heart Association Science Advisory urged physicians to begin screening of high-risk patients with a personal or family history of vascular disease. Unfortunately, other than suggesting that people increase their intake of foods high in B vitamins, they did not advise the use of supplements. However; certain physicians like Dr. A. DeMaria who is the associate editor for *Health News* recommends that everyone with heart disease or is at increased risk, take a multivitamin supplement containing all the B vitamins. This kind of advice is, unfortunately, rarely given despite the evidence that this inexpensive procedure could save thousands of lives and millions of dollars.

Checking Homocysteine Levels

The advice regarding screening is also contradictory. One report indicated that cases of multiple failed angioplasty are more likely related to high homocysteine levels than elevated LDL. In one such case, although LDL was within normal limits, homocysteine was 30 μmol/L. No wonder this expensive, invasive procedure sometimes proves ineffective. Elevated homocysteine should also be suspected if vascular pathology is apparent and standard blood tests prove unrevealing. Anyone that has cardiovascular disease or is at increased risk should have their homocysteine levels checked annually, especially if they are considering surgery. Patients with a family history of Alzheimer's, Lupus, diabetes or other chronic disease are also advised to have their homocysteine levels evaluated. Those who are taking supplements to control or lower homocysteine levels also need to have regular measurements taken to gauge therapeutic efficacy.[50] Appropriate nutritional management including adequate supplement dosages can

then be evaluated, and the subsequent benefit maintained.

Although the test for homocysteine is not considered inexpensive, the subsequent reduction in homocysteine from treatment is effective and safe. Therefore, regular screening for elevated homocysteine levels and concurrent treatment with appropriate vitamin supplementation should be considered as one of the most important measures that a clinician could implement to significantly lower the risk of developing potentially life-threatening degenerative disease attributable to chronic homocysteinemia.

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