# Homocysteine Reduction

Homocysteine is an amino acid made from a common dietary amino acid, methionine, that inflicts damage to the inner arterial lining (endothelium) and contributes to many diseases:

- cardiovascular disease
- congestive heart failure
- stroke
- migraines
- age-related macular degeneration
- hearing loss
- brain atrophy
- Alzheimer's disease

Fortunately, **B vitamins like folate, vitamins B6 and B12**, and other integrative interventions can reduce homocysteine and counteract this destructive process.

## Causes of High Homocysteine Levels (Hyperhomocysteinemia)

Many factors contribute to high homocysteine levels:

- Insufficient folate, vitamin B6, vitamin B12, betaine, vitamin B2, and magnesium
- Prescription drug use (including cholestyramine, colestipol, fenofibrate, levodopa, metformin, methotrexate, niacin, nitrous oxide, pemetrexed, phenytoin, sulfasalazine)
- High-methionine diet (including red meat and dairy products)
- Smoking
- Coffee
- Alcohol consumption
- Advancing age
- Obesity
- Genetic variant that causes an impaired ability to metabolize active folate from folic acid

**Note:** Life Extension believes that the optimal range for homocysteine levels is <8 µmol/L, much lower than the currently accepted <15 µmol/L.

## Dietary and Lifestyle Changes

Several dietary and lifestyle changes can help reduce chronic inflammation:

- Avoid methionine-rich foods like red meat and dairy products
- Exercise, as patients in a cardiac rehabilitation program showed a reduction in homocysteine from exercise alone
- Decrease or eliminate alcohol and smoking

## Integrative Interventions

- **B vitamins:** Folate, along with vitamins B6 and B12, has been shown in numerous studies to help lower homocysteine levels. The active form of folate, L-methylfolate, can achieve plasma folate levels up to 700% higher than synthetic folic acid and therefore may be more effective at lowering homocysteine levels.
- **Betaine (TMG) and Choline:** Higher intakes of TMG and choline (which is converted to TMG in the body) are related to lower circulating homocysteine concentrations.
- **N-acetyl L-cysteine (NAC):** NAC may displace homocysteine from its protein carrier, which lowers homocysteine and promotes the formation of cysteine and glutathione, a powerful antioxidant.
- **S-adenosylmethionine (SAMe):** Supplementing with SAMe promotes the conversion of homocysteine to cysteine, which is then converted to glutathione and lowers homocysteine levels.
- **Taurine:** Research suggests taurine can block methionine absorption (which is converted to homocysteine in the body) and produce a significant decline in homocysteine levels in 4 weeks.

# Introduction

Homocysteine is an amino acid that inflicts damage to the inner arterial lining (endothelium) and other cells of the body.

In 1968, a Harvard researcher observed that children with a genetic defect that caused them to have sharply elevated homocysteine levels suffered severe atherosclerotic occlusion and vascular disorders similar to what is seen in middle-aged

patients with arterial disease. This was the first indication that excess homocysteine might be an independent risk factor for heart disease.

Life Extension has identified elevated homocysteine as one of 17 independent risk factors for cardiovascular disease, anyone of which can initiate and propagate vascular disease. Among such risk factors, homocysteine's role in cardiovascular and cerebrovascular disease continues to be misunderstood by mainstream medicine.

Much of this confusion stems from highly publicized results of clinical trials that used B vitamins to reduce blood levels of homocysteine yet failed to prevent cardiovascular events in people with advanced atherosclerosis.[1,2] Life Extension believes these studies were seriously flawed, most notably because they used doses of B vitamins that were too low to reduce homocysteine to Life Extension's recommended optimal range of <8 µmol/L. At present, medical testing laboratories consider a homocysteine number between 11–15 µmol/L as the upper limit of "normal" despite robust clinical data to the contrary.[3,4] Consequently, many doctors remain misinformed as to the optimal target range for homocysteine and the doses of homocysteine-lowering nutrients required to achieve this optimal range.

## Homocysteine Basics

All homocysteine in the body is biosynthesized from methionine, an essential amino acid found abundantly in meats, seafood, dairy products, and eggs. Vegetables, with few exceptions (eg, sesame seeds and Brazil nuts), are low in methionine; even such protein-rich legumes as beans, peas, and lentils contain relatively small amounts of methionine compared to animal-derived foods.

Homocysteine exists in several forms[5]; the sum of all homocysteine forms is termed 'total homocysteine.' Protein-rich diets contain ample amounts of methionine and consequently produce significant levels of homocysteine in the body.[6]

Homocysteine is metabolized through two pathways: remethylation and transsulfuration. Remethylation requires folate and B12 coenzymes; transsulfuration requires pyridoxal-5'-phosphate, the B6 coenzyme.[7]

### Homocysteine Metabolic Pathways

The remethylation pathway requires vitamin B12, folate, and the enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR). In kidney and liver, homocysteine is also remethylated by the enzyme betaine homocysteine methyltransferase (BHMT), which transfers a methyl group to homocysteine via the demethylation of betaine to dimethylglycine (DMG). The transsulfuration pathway requires the enzyme cystathionine-synthase (CBS) and vitamin B6 (pyridoxal-5'-phosphate). Once formed from cystathionine, cysteine can be utilized in protein synthesis and glutathione (GSH) production.

Active folate, known as 5-MTHF or 5-methyltetrahydrofolate, works in concert with vitamin B12 as a methyl-group donor in the conversion of homocysteine back to methionine.

Normally, about 50% of homocysteine is remethylated; the remaining homocysteine is transsulfurated to cysteine, which requires vitamin B6 as a co-factor. This pathway yields cysteine, which is then used by the body to make glutathione, a powerful antioxidant that protects cellular components against oxidative damage.

Vitamin B2 (riboflavin) and magnesium are also involved in homocysteine metabolism. Thus, a person needs several different B-vitamins to help keep homocysteine levels low and allow for it to be properly transformed into helpful antioxidants like glutathione. Without B6, B12, B2, folate, and magnesium, dangerous levels of homocysteine may build up in the body.

Blood levels of total homocysteine increase throughout life in men and women.[8] Prior to puberty, both sexes enjoy optimally healthy levels (about 6 µmol/L). During puberty, levels rise, more in males than females,[9,10] reaching, on average, almost 10 µmol/L in men and more than 8 µmol/L in women. As we age, mean values of homocysteine continue to rise and the concentrations usually remain lower in women than in men.[11]

The higher total homocysteine concentrations seen in the elderly may be caused by many factors including malabsorption of B12 or a suboptimal intake of B vitamins (especially vitamin B12), reduced kidney function, medications that reduce the absorption of vitamins (as in the case of H2 receptor antagonists or proton-pump inhibitors reducing B12 absorption)[12] or increase the catabolism of the vitamins (as in the case of metformin reducing blood levels of B12 and folic acid).[13] Certain diseases are associated with higher homocysteine levels, as can such lifestyle factors as smoking,[14] coffee consumption,[15] and excessive alcohol intake.[16] Lack of exercise, obesity, and stress are also associated with hyperhomocysteinemia.

## What Is a Healthy Homocysteine Number?

Clinical testing laboratories consider a homocysteine value between 5 to 15 µmol/L as healthy. Life Extension believes that an upper limit of 15 µmol/L is too high for optimal health. Studies indicate adults with homocysteine values ≥6.3 µmol/L are at increased risk of atherosclerosis (Homocysteine Studies Collaboration), heart attack and stroke.[17] Homocysteine levels in the blood can increase due to age,[18] prescription drug use (see the "Drugs that Raise Homocysteine Levels" section), declining ability to absorb vitamin B12,[19] deteriorating kidney function,[20] smoking,[14] alcohol,[16] coffee consumption,[21] obesity,[22] declining

levels of physical activity,[4] and inheriting a genetic polymorphism known as the MTHFR C677T variant in methylenetetrahydrofolate reductase (MTHFR).[23] After age 50, a more practical target value for homocysteine is <8 µmol/L. Depending upon other factors, you may require larger-than-usual intakes of B vitamins to achieve a healthy blood level of homocysteine. Data from published studies reveal that there is no safe "normal range" for homocysteine. Epidemiological studies have shown that higher homocysteine levels are associated with higher risk, even at levels that are considered "normal."[24] Life Extension recommends a target of <8 µmol/L because published data, as well as our experience with homocysteine in tens of thousands of customers over more than 30 years, indicate that this threshold target is a realistic goal when taking optimal amounts of vitamins B6, B12, folate, TMG, and other homocysteine-lowering nutrients.[25]

The MTHFR C677T gene polymorphism is the single most important genetic determinant of blood homocysteine values in the general population. More than 40% of Hispanics and between 30–38% of whites living in the United States inherit at least one copy of this gene,[26] which impairs their ability to fully activate (methylate) folic acid to 5-methyltetrahydrofolate, the bioactive form of the B vitamin. Individuals who inherit this gene variant from both parents have a significantly higher (14–21%) risk of vascular disease than those who do not.

For this affected group, taking the bioactive folate supplement, 5-MTHF, may be a better strategy. 5-MTHF is clinically tested, is highly bioavailable,[27] can cross the blood–brain barrier,[28] and is unlikely to mask a vitamin B12 deficiency as folic acid can do.[29] Those who carry this gene variant can safely reduce their risk of homocysteine-related health problems using an inexpensive, nonprescription natural folate supplement.

# Homocysteine And Health

## Homocysteine and Alzheimer's Disease

In a 2002 study published in the *NewEngland Journal of Medicine,* dementia developed in 111 study participants of which 83 were diagnosed with Alzheimer's disease over an eight-year follow up. In those with a plasma homocysteine level greater than 14 µmol/L, the risk of Alzheimer's disease nearly doubled. Investigators concluded, "*An increased plasma homocysteine level is a strong, independent risk factor for the development of dementia and Alzheimer's disease.*"[30]

## How Elevated Homocysteine Leads to Vascular Damage

If unhealthy levels of homocysteine accumulate in the blood, the delicate lining of an artery (endothelium) can be damaged.

Homocysteine can both initiate and potentiate atherosclerosis. For example, homocysteine-induced injury to the arterial wall is one of the factors that can initiate the process of atherosclerosis, leading to endothelial dysfunction and eventually to heart attacks and strokes.[31,32] Several studies have shown that homocysteine can inflict damage to the arterial wall via multiple destructive molecular mechanisms.[19,33,34]

## Homocysteine Is Linked to Congestive Heart Failure

Small clinical studies have shown that patients with congestive heart failure (CHF) suffer from elevated plasma homocysteine levels.[35] Based on preclinical evidence that the myocardium may be especially susceptible to homocysteine-induced injury[36] and based on observations linking homocysteine to oxidative stress[37] and to left ventricular remodeling,[38,39] it has been hypothesized that elevated plasma homocysteine levels would increase the risk of CHF. Accordingly, researchers investigated the relationship of plasma homocysteine concentration to the risk of CHF in a community-based sample of adults (2,491 adults, mean age 72 years, 1,547 women) who participated in the well-known Framingham Heart Study during the 1979–1982 and 1986–1990 examination periods and who were free of CHF or prior myocardial infarction at baseline. In one study that examined patients without any manifestation of coronary heart disease at baseline, investigators found that the association of plasma homocysteine levels with risk of CHF was maintained in men and women and concluded "*an increased plasma homocysteine level independently predicts risk of the development of CHF in adults without prior myocardial infarction.*"[40]

## Reducing Homocysteine for Migraine Relief

Migraine is a debilitating disease that can be associated with elevated blood levels of homocysteine.[41-43]

A study showed that treatment with B-complex vitamins, including 5-MTHF, could provide relief for migraine sufferers including those with the MTHFR C677T genotype,[44] which typically limits the clinical effectiveness of supplemental folic acid since individuals with this genotype do not effectively convert folic acid to its active form. People with the C677T genotype consistently have higher levels of homocysteine than those with the normal C677C genotype. Headache frequency and pain severity were also reduced. The treatment proved successful in reducing homocysteine levels and migraine disability in study participants with the MTHFR C677T genotype. Researchers have long suspected that migraine headaches have a genetic component because migraine sufferers often have family members who also have the condition. Studies suggest up to 12% of those living in the United States and Western Europe have this genetic link to migraine.[45]

## Homocysteine's Role in Macular Degeneration

Studies of homocysteine's role in age-related macular degeneration (AMD: both wet and dry types) reveal a strong link between the compound and the disease.

In a group of 2,335 study participants who had evidence of AMD as detected from retinal photographs, researchers found that homocysteine blood levels >15 µmol/L were associated with an increased likelihood of AMD in participants aged <75 years. They also found a similar association for blood levels of vitamin B12 <125 pmol/L among all study participants. In participants with homocysteine levels ≤15 µmol/L, *low serum B12 was associated with nearly fourfold higher odds of AMD*.[46]

In a larger and more recent study, Harvard researchers enrolled 5,442 women who were at high risk for cardiovascular disease. The women were given a placebo or 2.5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12 per day. After an average of more than seven years of treatment and follow-up, researchers recorded 55 cases of AMD in the B-vitamin treatment group and 82 in the placebo group. Investigators concluded that in women at high risk of cardiovascular disease, daily long-term supplementation with folic acid, B6, and B12 may reduce the risk of AMD.[47]

## Homocysteine Linked to Hearing Loss

A number of published studies suggest hearing loss may be linked to plasma homocysteine levels, which could be reduced by folic acid supplementation.

One study conducted from September 2000 to December 2004 in 728 older men and women in the Netherlands (which does not have mandatory folic acid fortification) found that at initiation, the median threshold for hearing in the low frequency range (0.5 to 2 kHz) was 11.7 decibels (dB), and 34.2 dB in the high frequency range (4 to 8 kHz). By the end of the study, the thresholds had increased for both folic acid and placebo groups. In other words, a louder noise was required to get study participants to hear it. However, the increase was lower in the supplemented group in the low frequency range (1.0 vs. 1.7 dB increase for folic acid and placebo groups, respectively). There was no significant difference in threshold decline in the higher frequency region. Thus, folic acid supplementation slowed the decline in hearing of the speech frequencies typically associated with aging.[48]

Researchers studied the levels of homocysteine in 28 male patients (mean age 37) with noise-induced hearing loss. Homocysteine levels of subjects with noise-induced hearing loss were significantly higher compared to healthy controls, suggesting a causal link between increased homocysteine levels and noise-induced hearing loss.[49]

## Flawed Studies Lead to Confusion over B-Vitamins and Heart Disease

A 2010 review of several large randomized, double-blind, placebo-controlled trials that used various B-vitamin therapies for reducing cerebrovascular risk (VISP study)[50] and secondary cardiovascular disease risk (HOPE 2,[51] NORVIT,[52] WAFACS,[53] and WENBIT[54] studies) concluded that B-vitamin treatments effectively decrease plasma homocysteine levels and stroke risk, although such treatments failed to reduce cardiovascular risk.[2] A meta-analysis of randomized clinical trials comprising 16,958 participants with preexisting vascular disease found that folic acid supplementation had no effect on the risk of cardiovascular disease or all-cause mortality.[55]

Critical examinations of such studies that failed to show a reduction of cardiovascular events in patients treated with B vitamins have revealed numerous design and methodological flaws including limited statistical power, relatively short duration of follow-up, and insufficient number of cardiovascular events.[56-58] In addition, three of the studies were secondary prevention trials and therefore were not designed to test the ability of B vitamins to prevent heart attacks in healthy people. The most egregious flaw in these trials, however, is that *they all failed to use high enough doses of B vitamins to reduce study participants' homocysteine levels to the optimal target range of <8 µmol/L*.

Additional B-vitamin studies in patients undergoing balloon angioplasty and vascular stenting reveal the critical importance of lowering homocysteine levels to Life Extension's recommended optimal target range. Two studies that failed to use high enough doses of folic acid, B6, and/or B12 to achieve optimal homocysteine reduction saw restenosis rates rise in some patients who received vitamin therapy.[59,60] In contrast, a prospective, double-blind, randomized trial (the "Swiss Heart Study") examined the effects of folic acid, vitamin B6, and vitamin B12 treatment in 553 patients who underwent angioplasty.[61] Investigators observed a significant reduction in the need for revascularization of the target lesion at 1 year (9.9% in the treatment group vs. 16.0% in the control group). Significantly, the Swiss Heart Study is the *only* randomized controlled trial to date in which treatment reduced study participants' average plasma homocysteine levels (7.5 µmol/L) to within the range recommended by Life Extension (<8 µmol/L).

## Stroke Protection from B-Vitamin Therapy

The 2009 HOPE-2 trial for homocysteine therapy and stroke risk, which randomized 5,522 adults with known cardiovascular disease to a daily treatment regimen of B-vitamin therapy (2.5 mg folic acid, 50 mg vitamin B6, and 1 mg vitamin B12) for five years, *achieved reduction in stroke risk of 25%*.[51] HOPE-2 was the first large randomized, double blind, placebo-controlled trial to use clinically adequate doses of vitamin B12. It included high-risk participants with and without history of cerebrovascular disease drawn from countries with and without folic acid food fortification. *Significantly, homocysteine concentration decreased by 2.2 µmol/L in the B-vitamin therapy group and increased by 0.80 µmol/L in the placebo group*.

Another meta-analysis that focused on a subset of seven of 12 randomized studies added a randomized trial from China to assess the efficacy of folic acid supplementation in stroke prevention. Study investigators found that folic acid supplementation significantly reduced the risk of stroke by 18%.[62]

## Additional Studies on Homocysteine Reduction and Vascular Disease

A number of controlled studies that found positive effects of B-vitamin therapy on vascular disease yielded the following results:

- Folate supplementation improved arterial function in patients with peripheral arterial disease.[63] Two measures of arterial health, brachial pressure index (ABPI) and pulse wave velocity (PWV), were measured; ABPI improved significantly in all patients receiving folate compared with controls, while PWV improved significantly in individuals receiving an active form of folic acid (5-MTHF), and tended to be improved in those taking folic acid, compared with controls.
- Twenty hypercholesterolemic adults taking Lovastatin were given a daily folate supplement (5 mg) for eight weeks while 20 patients received a placebo[64]; only the folate-supplemented group experienced decreased blood levels of homocysteine.
- Reducing blood levels of homocysteine through B-vitamin therapy was shown to improve endothelial function in renal transplant recipients with hyperhomocysteinemia.[65] Investigators assigned 36 stable renal transplant recipients with hyperhomocysteinemia to either a B-vitamin treatment group (5 mg folic acid, 50 mg vitamin B6, and 1,000 mcg vitamin B12 per day) or to a control group (placebo only) for six months. Investigators found that homocysteine significantly decreased in the B-vitamin treatment group compared with baseline (12.6 vs. 20.1 µmol/L); no significant changes in homocysteine levels were observed in the control group. Vasodilatation responses were significantly improved in the treatment group compared to controls.
- Folic acid treatment in patients undergoing hemodialysis (10 mg three times weekly after dialysis treatment for six months) lowered plasma homocysteine levels while it significantly increased total plasma antioxidant capacity levels.[66] Twenty patients receiving placebo treatment showed no statistically significant effect on any of the parameters studied.
- A study treated liver transplant recipients with 5-methyltetrahydrofolate (5-MTHF; 1 mg) versus folic acid (1 mg) versus placebo in an 8-week double-blind placebo-controlled trial. Investigators observed a significant decrease of total serum homocysteine in the 5-MTHF group by week 8; they found no significant decrease of total serum homocysteine in either the folic acid group or the placebo group. The effects of 5-MTHF (active folate) were found to be significantly more potent than folic acid at lowering elevated homocysteine levels in liver transplant recipients.[67]
- A randomized study in 103 patients at increased risk of heart attack or stroke investigated the effect of daily supplementation of folic acid (5 mg) on carotid artery intima-media thickness (IMT). Study participants were randomized to receive either a daily dose of 5 mg folic acid or placebo. After 18 months of folic acid supplementation, participants in the active treatment group saw their homocysteine levels significantly reduced, compared to a significant increase in the placebo group. *Investigators noted significant regression of carotid IMT in the treatment group* compared to significant IMT progression in the placebo group.[68]
- A controlled study was carried out to assess whether folic acid supplementation could produce a reduction in homocysteine levels and improvement in endothelial function in patients with unstable angina (UA) and hyperhomocysteinemia.[3] Investigators treated patients with 5 mg of folic acid for eight weeks, rechecking homocysteine, folic acid, and vitamin B12 levels at the end of four and eight weeks. Plasma homocysteine levels were significantly higher in patients with UA than in patients without UA at baseline (19.2 vs. 10.7 µmol/L), whereas plasma levels of folic acid and vitamin B12 were significantly lower. After eight weeks of folic acid supplementation, homocysteine levels were reduced by 55.3% in the 22 UA patients with hyperhomocysteinemia. Flow-mediated dilation, an indirect measure of endothelial function, also improved significantly after eight weeks of treatment with folic acid.
- A 2008 study examined carotid artery atherosclerosis as determined by measurements of carotid IMT and plaque calcification in 923 patients with vascular disease or diabetes.[69] Study investigators found an inverse association between plasma folate and plaque calcification score; there was a trend toward an inverse association with IMT as well.

# Dietary and Lifestyle Considerations

- **Avoid methionine-rich foods**, particularly red meats and dairy products. Although methionine is an essential amino acid, it is also suspected to indirectly promote atherosclerotic plaque growth by increasing homocysteine levels.
- **Exercise.** In a cardiac rehabilitation program following bypass surgery, angioplasty, or heart attack, 76 participants experienced a modest 12% reduction in homocysteine just by engaging in a program of regular exercise.[70]
- **Decrease or eliminate alcohol, coffee** (filtered and unfiltered), **and smoking**.
- **Weight loss.** Obesity is associated with higher homocysteine.

# Targeted Natural Strategies

## N-Acetyl-Cysteine

Research studies have documented the homocysteine-lowering effect of the nutraceutical, N-acetyl-cysteine (NAC), which can lead to a highly significant reduction in cardiovascular events, owing to the ability of NAC to lower plasma homocysteine levels and improve endothelial function. Researchers believe that NAC displaces homocysteine from its protein carrier in the blood.

This promotes the formation of cysteine and NAC disulfide molecules with high renal clearance, thereby removing homocysteine from plasma.[71,72]

- A 2007 study randomized 60 patients with hyperhomocysteinemia and confirmed coronary artery disease to 5 mg folic acid, 600 mg NAC, or placebo daily for eight weeks. Folic acid and NAC supplementation both lowered homocysteine levels and improved endothelial function. Folic acid decreased homocysteine from 21.7 µmol/L to 12.5 µmol/L and NAC decreased homocysteine from 20.9 µmol/L to 15.6 µmol/L. Both treatments improved endothelium-dependent dilation compared to placebo.[73]
- In a double-blind crossover design study, Swedish investigators gave NAC supplements to 11 patients with high plasma lipoprotein(a), which is an independent risk factor for cardiovascular disease.[74] While investigators observed no significant effect on plasma lipoprotein(a) levels, they did find that plasma levels of homocysteine were significantly reduced during treatment with NAC by *an astounding 45%*.
- One study examined the effect of oral NAC supplementation in nine young healthy females and found that the supplement induced a rapid and significant decrease in plasma homocysteine levels and an increase in whole blood concentration of the antioxidant glutathione. Study investigators concluded that NAC might therefore be a highly efficient nutraceutical for reducing blood levels of homocysteine.[75]

## Omega-3 Polyunsaturated Fatty Acids (PUFAs)

A growing body of research on marine lipids, rich in omega-3 polyunsaturated fatty acids (PUFAs), reveals that omega-3 rich fish oil supplementation can reduce elevated homocysteine levels:

- A 2010 animal model study examined the effect of fish oil rich in omega-3 PUFAs on homocysteine metabolism. Three groups of randomly divided rats were fed olive oil, tuna oil, or salmon oil for eight weeks. The level of plasma homocysteine was significantly decreased only in the group fed tuna oil, rich in omega-3 PUFAs. It is not clear why the salmon oil did not reduce homocysteine as it too is rich in omega-3 PUFAs.[76]
- A 2009 randomized double-blind placebo-controlled clinical trial conducted on 81 patients with type 2 diabetes assigned each patient either three capsules of omega-3 fatty acids (3 grams) or a placebo every day for a period of two months. Homocysteine levels in the treatment group declined as much as 3.10 µmol/L; glycolsylated hemoglobin (HbA1C, a measure of long-term sugar levels in the blood) decreased in the treatment group and increased in the control group.[77]

## Taurine

Supplementing with the amino acid taurine can protect against coronary artery disease by favorably modulating blood levels of homocysteine. Research suggests taurine can block methionine absorption from the diet, thereby reducing available substrate for homocysteine synthesis.[78] One animal study found that taurine normalized hyperhomocysteinemia and reduced atherosclerosis by 64% over control animals and reduced endothelial cell apoptosis by 30%.[79] Study investigators also observed that taurine supplementation reduced left main coronary artery wall pathology due to a favorable effect on plasma total homocysteine and apoptosis.

A study of 22 healthy middle-aged women (33 to 54 years) found that after taurine supplementation (3 grams per day for four weeks), plasma homocysteine levels exhibited a significant decline, *from 8.5 µmol/L to 7.6 µmol/L*. The investigators concluded that sufficient taurine supplementation might effectively prevent cardiovascular disease.[80]

## Trimethylglycine (TMG) and Choline

TMG was originally called betaine after its discovery in sugar beets in the 19th century. TMG serves as a methyl donor in a reaction converting homocysteine to methionine. It is commonly used for reducing high homocysteine levels though it has yet to be effectively studied to determine its full cardiovascular benefits through its ability to lower homocysteine.[81]

A 2009 study examined the effect of betaine (TMG) supplementation on atherosclerotic lesion progression in apolipoprotein E-deficient mice.[81] After a 14-week treatment with TMG, analyses revealed that the higher dose of TMG was related to smaller atherosclerotic lesion area. Compared with mice not treated with TMG after 14 weeks, mice receiving 1%, 2%, or 4% TMG had 10.8%, 41%, and 37% smaller lesion areas, respectively. TMG supplementation also reduced aortic expression of the inflammatory cytokine, tumor necrosis factor-alpha (TNF-α), in a dose-dependent way. These data suggest in addition to its homocysteine-lowering action, TMG may also exert its anti-plaque effect by inhibiting aortic inflammatory responses mediated by TNF-α.

Data from the Framingham Offspring Study found that intakes of TMG and choline (choline is metabolized to TMG in the body) were inversely related to circulating homocysteine concentrations, particularly among participants with low folate intake or among those who consumed alcoholic beverages.[82] Other studies have shown that choline deficiency in mice and humans is associated with increased plasma homocysteine levels after consuming methionine.[83] A Finnish study of TMG supplementation showed a daily supplement of 6 grams TMG for 12 weeks reduced blood homocysteine values in healthy subjects by approximately 9%.[84]

## S-Adenosyl-L-Methionine (SAMe)

SAMe (S-adenosyl-L-methionine), biosynthesized from methionine and ATP, functions as a primary methyl group donor in a variety of reactions in the body and is directly involved in homocysteine synthesis and metabolism. Taking supplemental SAMe promotes the conversion of homocysteine to cysteine and glutathione, thus lowering homocysteine levels.[85] One study found that taking SAMe supplements increased the activity of 5-MTHF, a major co-factor involved in the metabolism of homocysteine.[86]

In effect, SAMe acts as a 'switch' to control enzymes involved in the remethylation and transsulfuration pathways of homocysteine metabolism.[87] Since some of the SAMe's methyl groups are used in the body's production of creatine (an energy substrate used primarily by skeletal muscle), it has been suggested that supplementing one's diet with creatine would free up SAMe's methyl groups to favorably modulate homocysteine levels.[88] One study found that lab animals maintained on creatine-supplemented diets exhibited significantly lower (~25%) plasma homocysteine levels than controls.[89] Those who use SAMe should make sure they are taking supplemental folate, B6 and B12 to ensure that SAMe promotes the conversion of homocysteine to beneficial compounds in the body.

## Riboflavin

Vitamin B2 (riboflavin) has long been known to be a determinant of plasma homocysteine levels in healthy individuals with the 5-MTHFR C677T gene variant that causes hyperhomocysteinemia.[90] Homocysteine is highly responsive to riboflavin (riboflavin is required as a co-factor by MTHFR), specifically in individuals with the MTHFR 677 TT genotype.[91]

A four-week, randomized, placebo-controlled, double-blind trial found that 10 mg/day oral riboflavin supplementation for 28 days lowered plasma homocysteine concentrations in 42 subjects (60 to 94 years) with low riboflavin status.[92]

## B Vitamins

A two-year randomized clinical trial (known as VITACOG) completed in 2010 found that the accelerated rate of brain atrophy in elderly patients suffering from mild cognitive impairment could be significantly slowed by treatment with homocysteine-lowering B vitamins.[93]

Researchers at Oxford University, UK randomized study participants to receive either placebo or a combination of folic acid (0.8 mg/d), vitamin B12 (0.5 mg/d), and vitamin B6 (20 mg/d) for 24 months. A subset of participants agreed to have cranial MRI scans at the start and finish of the study for the purpose of measuring the change in rate of atrophy of the entire brain.

A total of 168 participants (85 in active treatment group; 83 receiving placebo) completed the MRI section of the trial. Results showed that the B-vitamin treatment response was related to baseline homocysteine levels: Participants in the B-vitamin treatment group with the highest levels of homocysteine (≥ 13.0 µmol/L) at the start of the trial experienced half the brain shrinkage over two years compared to those participants with the highest homocysteine blood levels at the start of the trial and who received the placebo.

This important study demonstrated that the accelerated rate of brain atrophy seen in approximately 16% of elderly patients suffering from mild cognitive impairment[94] could be significantly slowed by simple treatment with folic acid and vitamins B6 and B12.

### Ordinary B-Vitamin Supplements and Folate-Rich Foods May Not Be Enough to Lower Homocysteine

Even though folic acid-fortified foods are ubiquitous, and despite peoples' best efforts to insure adequate intake of the vitamin through supplementation, many individuals run the risk of not obtaining sufficient amounts of folate necessary to achieve healthy blood levels of homocysteine unless they supplement with bioactive folate. Cooking and food processing destroy natural folates.95 Although red blood cells can retain folate for 40–50 days following discontinuation of supplementation, synthetic folic acid is poorly transported to the brain and is rapidly cleared from the central nervous system.[96]

Many people who take ordinary B-vitamin supplements are unable to sufficiently lower their homocysteine levels enough to prevent disease.[97] Fortunately, there is hope for those with seemingly intractable homocysteine levels. One study found that giving L-methylfolate (5-MTHF; also called *active folate*) to patients with coronary artery disease resulted in a *700-percent higher plasma concentration of folate-related compounds compared to folic acid*. This difference was irrespective of the patient's genotype.[27]

5- MTHF is the predominant biologically active form of folate in cells,[98] the blood,[99] and the cerebrospinal fluid.[96] Until recently, 5- MTHF was available only in prescription medicines and medicinal food products. Now, this active form of folate, which provides increased protection against homocysteine-related health problems, is available as a dietary supplement. This form of the vitamin is unlikely to mask a vitamin B12 deficiency, a well-known shortcoming of folic acid. Since 5-MTHF is *the only form of folate used directly by the body*, it does not have to be converted and metabolized to be clinically useful, as does synthetic folic acid.

Synthetic folic acid, as used in ordinary dietary supplements and vitamin-fortified foods, must first be converted in cells to active L-methylfolate in order to be effective. These steps require several enzymes, adequate liver and gastrointestinal function, and sufficient supplies of niacin (vitamin B3), pyridoxine (B6), riboflavin (B2), vitamin C, and zinc.[100]

The low dose requirements for 5-MTHF make it a relatively inexpensive supplement with superior clinical benefits over folic acid. People who would benefit from taking active folate include:

- Those who desire to take advantage of 5-MTHF as a part of their anti-aging strategy due to its potency, low cost, and bioavailability.
- Those with elevated risk factors for cardiovascular disease.
- Those taking drugs known to interfere with the absorption or metabolism of folate.
- People with the gene variant 5-MTHFR C677T.

Individuals with the 5-MTHFR C677T polymorphism are at higher risk of cardiovascular disease, stroke, preeclampsia (high blood pressure in pregnancy), and birth defects that occur during the development of the brain and spinal cord (neural tube defects). The mutation replaces the DNA nucleotide cytosine with thymine at position 677 in the MTHFR gene. (Nucleotides are the building blocks of DNA.) This change in the MTHFR gene produces a form of the enzyme, methylenetetrahydrofolate reductase, which is thermolabile, meaning its activity is reduced at higher temperatures.

A daily dose of 0.8 mg 5-MTHF is typically used in research studies to achieve a clinically beneficial reduction in elevated plasma homocysteine concentrations. In some cases, doses as low as 0.2 mg to 0.4 mg have been shown to achieve this effect.[101]

### Drugs That Raise Homocysteine Levels

A number of prescription drugs and natural compounds can elevate blood levels of homocysteine by interfering with folate absorption or metabolism of homocysteine. These include:

- **Caffeine**[102]: Cafcit, Cafergot, Esgic, Excedrin Migraine, Fioricet, Fiorinal, Norgesic, Synalgos-DC
- **Cholestyramine**[103]: Questran, Questran Light, Cholybar
- **Colestipol**[104]: Cholestid
- **Fenofibrate**[105]: Antara, Fenoglide, Lipofen, Lofibra, Tricor, Trilipix
- **Levadopa**[106]: Parcopa, Sinemet, Stalevo
- **Metformin**[107]: ActoPlus Met, Avandamet, Fortamet, Glucophage Glucovance, Glumetza, Janumet, Metaglip, Prandimet, Riomet
- **Methotrexate**[107]: Rheumatrex
- **Niacin**[107]: Advicor, Ocuvite, Cardio CitraNatal Basic, Heplive, Niaspan, Simcor
- **Nitrous oxide**[108]
- **Pemetrexed**[109]: Alimta
- **Phenytoin**[110]: Dilantin, Phenytek
- **Pyrimethamine**[111]: Daraprim, Fansidar
- **Sulfasalazine**[112]: Azulfidine

## What You Need To vKnow

- Elevated blood levels of homocysteine have been linked with a wide range of health disorders including heart disease, stroke, macular degeneration, hearing loss, migraine, brain atrophy, dementia and cancer.
- A high-protein diet, especially one that includes red meats and dairy products, is also high in methionine, the parent compound of homocysteine. Following such a diet can increase blood levels of homocysteine.
- Numerous factors, including prescription drug use, smoking, coffee and alcohol consumption, advancing age, genetics, and obesity contribute to elevated homocysteine levels.
- Many people carry a genetic variation that is linked with elevated homocysteine levels. People carrying this gene variant suffer from an impaired ability to metabolize folic acid to its active form, but may achieve a significant reduction in plasma homocysteine by taking an active folate (5-MTHF) supplement.
- Vitamin B2, B6, and B12 supplements as well as those containing choline and TMG work together with active folate to maintain homocysteine levels within a healthy range.
- As humans grow older, homocysteine levels increase substantially. However, although these increased levels are “normal,” they are still associated with higher risk of various health problems.
- Although some clinical testing laboratories consider homocysteine levels of up to 15.0 µmol/L as normal, Life Extension believes this is too high for optimal health and therefore recommends keeping homocysteine levels < 8 µmol/L.
- People taking active folate can achieve plasma folate levels 700% higher than by taking an ordinary folic acid27

supplement and may therefore more effectively lower elevated homocysteine levels.

A program of regular exercise may help people recovering from a heart attack, bypass surgery, or angioplasty to modestly reduce homocysteine levels.

## For More Information

To learn more about the conditions associated with hyperhomocysteinemia, see the following protocols:

- Heart Failure
- Atherosclerosis and Cardiovascular Disease
- High Blood Pressure
- Diabetes and Glucose Control
- Thyroid Regulation

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