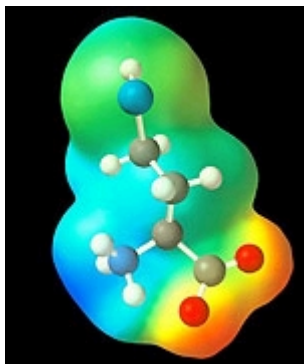


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## REPORT

## Nutritional Therapies for Managing Homocysteine

By William Davis, MD



Scientists have accumulated an immense amount of data associating excessive levels of homocysteine with coronary disease and other pathological conditions. Moreover, emerging research is uncovering important correlations between elevated homocysteine with chronic diseases such as macular degeneration, Alzheimer's disease, and osteoporosis.

In this article, we take a look at established research on the dangers of elevated homocysteine, as well as some of the more recent findings concerning this important marker of cardiovascular health. We also outline strategies that aging adults can use to lower homocysteine naturally, as well as our rationale for pursuing such a preventive approach.

Homocysteine is an amino acid that plays key roles in cellular metabolism and protein manufacture. At elevated levels in the body, however, homocysteine may have far-reaching, perhaps even deadly consequences, ranging from heart disease and stroke to osteoporosis and depression.

It is now widely accepted that food sources alone cannot consistently supply the levels of nutrients necessary to sustain optimal homocysteine metabolism. While the FDA has mandated folic acid fortification in wheat products, that is not nearly enough for many aging adults.

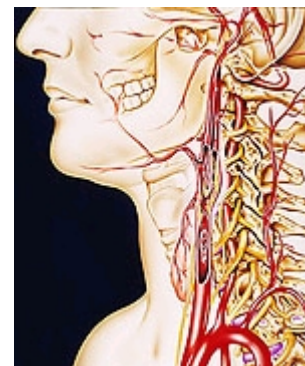
Emerging studies are uncovering novel nutritional strategies for lowering high homocysteine levels, offering new possibilities for effective control of this potentially lethal amino acid.

### HOMOCYSTEINE AND VASCULAR DISEASE RISK

Following the discovery of homocysteine in 1931, little was known about this amino acid for several decades. This changed in the 1960s, when Dr. Kilmer McCully of Harvard proposed that extraordinarily advanced atherosclerosis observed in children and teenagers suffering from heart attacks and stroke was due to an extreme excess of homocysteine. Blood levels of homocysteine in these unfortunate children ranged as high as 300 micromoles per liter ( $\mu\text{mol/L}$ ), high enough to be easily detected in the urine, thus the initial misnomer "homocystinuria." For years after his initial observations in children, and despite intense opposition, Dr. McCully argued that homocysteine was also a major risk factor for heart disease in the broader population.

Subsequent studies have confirmed Dr. McCully's proposition. An epidemiological study has demonstrated that homocysteine levels above 10  $\mu\text{mol/L}$  are associated with an up to threefold increase in heart attack risk.<sup>1</sup> Such levels are widespread, occurring in 5-10% of the US population and 40% of patients with vascular disease.<sup>2</sup> The risk from homocysteine is "continuous," having no threshold levels where risk suddenly develops. Instead, the higher your homocysteine level, the greater your risk. Levels commonly thought of as normal because they are average for Americans have been shown to contribute to heart disease and stroke risk. Levels as low as 9  $\mu\text{mol/L}$  carry long-term risk, with risk escalating even more sharply at levels of 15  $\mu\text{mol/L}$  or greater.<sup>3</sup> Unfortunately, many blood laboratories still consider "normal" levels to be 5-15  $\mu\text{mol/L}$ . Thus, if your doctor tells you your homocysteine level is "normal," you should ask, "How normal?"

Since Dr. McCully's initial observations, homocysteine has been tied to a constellation of biochemically related disorders. The lack of deep-pocketed drug company support has, to some degree, slowed the evolution of confirmatory clinical data. However, we are beginning to see the formation of a broad consensus across a variety of disease states. Homocysteine and a deficiency of the nutrients that lower it are taking center stage. Fortunately, treatment to lower excess homocysteine is inexpensive, safe, and readily available.



#### Vascular diseases.

Cutaway artwork of a blood clot (lower center) approaching a junction (center) of the left carotid artery that has been narrowed by atherosclerotic plaques (yellow). These are fatty deposits of cholesterol on the artery walls. They have caused narrowing of the artery, and if the blood clot lodges, then the oxygenated blood supply to the head and brain will be interrupted. This will cause a stroke, where the brain is damaged due to lack of oxygen. The backbone, its nerves (yellow), and skull

Homocysteine has been implicated in multiple stages of the process leading to coronary and arterial plaque growth and activity. Among the most important of the damaging effects observed are:

- Homocysteine induces the growth of vascular muscle cells, which are principal components of atherosclerotic plaque.<sup>4-6</sup> Elevated homocysteine levels stimulate production of interleukin-8 and monocyte chemoattractant protein-1, both of which are responsible for attracting inflammatory cells into the arterial wall.<sup>7,8</sup> Inflammation drives injury and plaque rupture, causing heart attack.<sup>9,10</sup>
- High homocysteine levels are associated with the oxidation of low-density lipoprotein (LDL) particles, a more damaging form of LDL.<sup>11-16</sup>
- Homocysteine may promote blood clot formation through various mechanisms that are still not well understood. It appears to have effects that increase clotting factors, increase tissue factor expression, increase platelet aggregation, and inhibit an anticoagulant protein called thrombomodulin. It may also cause abnormalities in the function of fibrinogen and thrombin generation.<sup>17-26</sup> Blood clot formation is the final step in heart attack after a plaque ruptures.

Homocysteine is an important marker of increased risk for both carotid and aortic plaque, both of which signal heightened risk for stroke. The higher your homocysteine level, the greater the extent of plaque in the aorta, the large artery that emerges from the heart.<sup>27,28</sup> The European Concerted Action Project reported more than a doubling of vascular disease when homocysteine levels exceed 12  $\mu\text{mol/L}$ .<sup>29</sup> For patients with coronary artery disease, homocysteine levels of 20  $\mu\text{mol/L}$  or higher predict a startling fivefold higher mortality risk compared to patients with a level of 9  $\mu\text{mol/L}$ .<sup>5</sup>

Does homocysteine cause heart attacks in humans? Substantial epidemiological observations show that the higher the homocysteine level, the higher the risk of heart attack. For example, a study reported in the *New England Journal of Medicine* followed 587 people with coronary disease, many of whom had undergone bypass surgery or angioplasty. Over the ensuing five years, the mortality rate of those with homocysteine levels below 9  $\mu\text{mol/L}$  was 3.8%. The mortality rate for those with homocysteine levels of 15  $\mu\text{mol/L}$  or greater was 24.7%—more than six times higher!<sup>5</sup> Similar observations have been made in several other large studies.<sup>31-33</sup>

### Homocysteine Levels Predict Atherosclerosis Progression

In a recent publication, researchers from UCLA and Johns Hopkins reported a relationship between elevated homocysteine levels and the progression of atherosclerotic plaques.

In patients with elevated homocysteine, the progression of coronary artery calcification (an indicator of atherosclerotic plaque burden) doubled within a 20-month period compared to that of individuals with lower homocysteine values.<sup>30</sup>

Among the newly emerging cardiovascular risk factors are homocysteine and C-reactive protein (CRP). Electron beam computed tomography (EBT) has also emerged as a useful tool to assess coronary artery calcification, and thereby measure atherosclerotic plaque burden and help predict the risk of future coronary events.

In their study, the UCLA-John Hopkins researchers enrolled 100 men and 33 women. All were without symptoms of coronary artery disease or kidney disease, and had undergone EBT scans within the previous 8-80 months. The participants received repeat EBT scans and their blood was tested for CRP, homocysteine, and other cardiovascular risk factors upon enrollment in the study.<sup>30</sup>

Participants whose homocysteine levels were equal to or greater than 12  $\mu\text{mol/L}$  were found to have a 35% mean increase in the progression of coronary artery calcification, compared to a 17% increase in those whose homocysteine levels were below 12  $\mu\text{mol/L}$ . No other factors considered in the study, such as cholesterol or body mass index, predicted coronary calcification progression. The authors concluded that elevated homocysteine “strongly and independently predicts progression of coronary plaque burden.”<sup>30</sup>

## GENDER, AGING, AND OTHER RISK FACTORS

Homocysteine levels increase gradually as we age, with an abrupt jump in females during the menopausal years. From early adulthood to the age of 60 and above, increases in homocysteine levels of 50–100% are often seen.<sup>34</sup> Increases of 2-5  $\mu\text{mol/L}$  are common over several years in both men and women, particularly after the age of 65. Therefore, a single favorable laboratory assessment does not necessarily mean that one’s homocysteine will not rise to dangerous levels several years later. It is advisable to re-test your homocysteine level every year, even if an initial reading is favorable.

Certain lifestyle factors may increase the risk of elevated homocysteine levels. Vegetarians, for example, tend to have 20-30% higher homocysteine levels than their meat-eating counterparts. This observation is likely due to less vitamin B12 intake in the vegetarian diet.<sup>35-36</sup> Smoking, excessive coffee consumption (more than 5-6 cups daily), and alcohol abuse can also raise homocysteine.<sup>37</sup>

Elevated homocysteine levels take on special significance in the presence of other risk factors for vascular disease. For example, Dutch researchers have shown that while a 5- $\mu\text{mol/L}$  increase in homocysteine in non-diabetics confers a 38% greater risk of cardiovascular disease, the same 5- $\mu\text{mol/L}$  increase in diabetics carries a 238% greater risk!<sup>38</sup> People who smoke have a tremendously magnified risk of cardiovascular disease in the presence of higher homocysteine levels. One study from Europe showed a 12-fold higher risk for cardiovascular disease in smokers with homocysteine levels above 12  $\mu\text{mol/L}$ .<sup>39</sup>

Other data show that the higher your homocysteine, the more it increases the dangers of other risk factors such as high cholesterol, magnifying risk several-fold.<sup>39</sup> A particularly lethal combination of risk factors is a high homocysteine level (in this study, above 12  $\mu\text{mol/L}$  for females and greater than 15  $\mu\text{mol/L}$  for males) combined with a lipoprotein(a) level of greater than 40 mg/dL.<sup>40</sup>

## DOES TREATMENT REDUCE RISK?

Researchers in Ontario, Canada, reported that a homocysteine level above 14  $\mu\text{mol/L}$  identified a group showing much more rapid growth of carotid plaque; however, treatment with 2500 mcg of folic acid, 25 mg of vitamin B6, and 250 mcg of vitamin B12 daily completely eliminated any further plaque growth.<sup>41</sup> Dutch researchers have reported extensively on treating high homocysteine levels using folic acid and vitamin B6 in patients with peripheral arterial disease (usually of the leg arteries), demonstrating reduction of heart attack risk and slowed growth of carotid and leg artery plaque.<sup>42,43</sup>

In a Swiss study, 553 patients were given a placebo or 1000 mcg of folic acid, 10 mg of B6, and 400 mcg of B12 daily following coronary angioplasty. After six months, 9.9% of the patients receiving the B vitamins had to undergo a repeat procedure for re-growth of blockage or a new blockage, while 16.0% of placebo patients required another procedure. Overall cardiac events, including death, were reduced from 22.8% in the placebo group to 15.4% in the B-vitamin group. Interestingly, both groups started with a homocysteine level of only 11.0  $\mu\text{mol/L}$ , which was reduced to 7.2  $\mu\text{mol/L}$  with B vitamins.<sup>44</sup> Another trial of folic acid alone (5 mg daily) versus placebo in 283 Dutch patients—all heart attack survivors—yielded conflicting results. All the participants took a cholesterol-lowering medication along with folic acid or placebo. This trial revealed no benefit of folic acid in addition to the cholesterol drug over a one-year period.<sup>45</sup>



**Narrowed carotid artery.** Colored three-dimensional computed tomography (CT) scan of the interior of a 59-year-old patient's carotid artery, showing stenosis (narrowing). The carotid artery supplies blood to the head. The artery has become narrowed by fatty deposits (yellow) that thicken the inner coating of the arteries.

A carotid ultrasound study showed that supplementation with 2500 mcg of folic acid, 25 mg of vitamin B6, and 250 mcg of vitamin B12 daily achieved modest regression of carotid plaque. Two groups were examined: those with baseline homocysteine levels above 14  $\mu\text{mol/L}$  and those with levels below 14  $\mu\text{mol/L}$ . Participants with higher homocysteine levels achieved greater regression using supplements, but even the group with initial levels below 14  $\mu\text{mol/L}$  obtained plaque regression, suggesting that ideal homocysteine levels are well below 14  $\mu\text{mol/L}$ .<sup>41</sup>

A study from Wake Forest University produced somewhat conflicting results. A comparison of a so-called "high-dose" B-vitamin formulation of 2500 mcg of folic acid, 25 mg of vitamin B6, and 400 mcg of vitamin B12 versus a "low-dose" regimen of 200 mcg of folic acid, 0.2 mg of B6, and 6 mcg of B12 showed no difference in stroke or heart attack risk over two years. In this study comparing "low-dose" to "high-dose" vitamins, the baseline average homocysteine reading was 13.4  $\mu\text{mol/L}$  of blood. The "low-dose" vitamin group experienced very little change in homocysteine levels after two years. The so-called "high-dose" arm (which did not provide particularly high doses) declined from the baseline of 13.4  $\mu\text{mol/L}$  to 11.0  $\mu\text{mol/L}$ . This decline was not enough to bring these so-called "high-dose" subjects into the safe homocysteine range needed to reduce stroke risk.<sup>46</sup>

Despite the strong epidemiological association between homocysteine and heart attack and stroke risk, the treatment trials still need to better define how best to manage vitamin replacement. Studies that include participants with higher homocysteine levels are needed in order to generate statistically meaningful results. Most of the participants in studies that failed to show benefit had low homocysteine levels. It is therefore no surprise that a treatment benefit over a brief time period might not be measured. Imagine giving an antibiotic to people whether or not they had an infection. No benefit would likely be measured because of a dilutional effect of treating people without infection. Additional trials may shed further light on these questions. However, the association between homocysteine and disease is so overwhelmingly strong that most authorities agree that treatment is readily justified and advisable.



# REPORT

## Nutritional Therapies for Managing Homocysteine

By William Davis, MD

### WAYS TO LOWER HOMOCYSTEINE NATURALLY

The potential benefits of nutritional homocysteine control are great, while the dangers are virtually nonexistent. Based on the weight of accumulated evidence, our clinic advocates lowering homocysteine levels above 7-8  $\mu\text{mol/L}$  using a graded dosing of three B vitamins, up to maximum doses of 5000 mcg of folic acid, 100 mg (occasionally even 500 mg under a doctor's supervision) of vitamin B6, and up to 1000 mcg of vitamin B12. Our treatment goal is to lower homocysteine to below 7  $\mu\text{mol/L}$ . We also advocate using choline and trimethylglycine (TMG or betaine) from food or nutritional supplements to augment the benefits of B vitamins and to more effectively suppress the after-meal surge in homocysteine that is not fully controlled by vitamins alone.

Your choices for controlling homocysteine include:

- **Folic acid.** Folic acid is the most important factor in controlling homocysteine. Although the US recommended daily allowance (RDA) for adults is only 400 mcg,<sup>47</sup> extensive survey data showed that an extraordinary 88% of US adults have a folic acid intake below the RDA.<sup>48</sup> Low folic acid intake by pregnant women carries a particularly dire risk, causing devastating neural tube defects in newborns. Low folic acid intake from diet is a growing problem because of food processing. This prompted the FDA to mandate folic acid fortification in enriched grain products.

Fortification provides an estimated extra 100 mcg of folic acid daily for most adults and does indeed result in modest reductions of about 0.5  $\mu\text{mol/L}$  in homocysteine. Nonetheless, obtaining sufficient quantities of folate (the food form of folic acid) from foods is difficult, and the majority of Americans not taking folic acid supplements have sufficiently low blood levels that allow higher homocysteine levels.<sup>49</sup> Keep in mind that folic acid supplements are twice as bioavailable as folate from food.<sup>50</sup> For example, 200 mcg of a folic acid supplement (as an individual supplement or added to grains) provides the same active quantity as 400 mcg of naturally occurring folate from food.<sup>51</sup> If you do not eat grain products or you have a higher level of homocysteine, specific folic acid supplementation beyond that in your diet will be necessary. A daily folic acid dose of 800 mcg may lower homocysteine by around 25%.<sup>52-53</sup> However, some doctors prescribe folic acid doses up to 5000 mcg for highly elevated homocysteine levels.

- **Vitamin B12.** Vitamin B12 deficiency is common and can contribute to rising homocysteine, particularly in people over 65. In rare cases, replacing folic acid alone can mask a latent B12 deficiency, resulting in nervous system disorders.

As a general rule, vitamin B12 and folic acid should be replaced together to maximize their homocysteine-lowering effects. Absorption of B12 is a little tricky, and in the past, physicians simply injected B12. However, more recent data suggest that a dose of 500-2000 mcg is every bit as good as an injection.<sup>54</sup> A recent dose-exploring trial established that even 500 mcg of B12 achieves the same effect in correcting B12 deficiency as injectable forms. If you are not B12 deficient (discuss this with your doctor), then lesser doses are sufficient. Our clinic commonly advises patients to take 250 mcg of B12 along with folic acid, a dose that provides about two thirds of the effectiveness of the higher doses.<sup>54</sup>

- **Vitamin B6.** Taken along with folic acid, vitamin B6 is effective in blocking post-meal surges of homocysteine, particularly when methio-nine-rich meats are part of the meal. Low blood levels of B6 are common, especially in people with higher homocysteine levels.<sup>55</sup> The precise dose of B6 required for maximum homocysteine lowering has been controversial, with doses of 2-50 mg commonly used in clinical studies. However, Dutch researchers who have extensive experience with homocysteine-lowering therapies routinely use 250 mg of B6 without ill effect.<sup>43,56,57</sup>

High-dose vitamin B6 (100-500 mg per day) has been used successfully in managing perimenstrual symptoms and carpal tunnel syndrome.<sup>58</sup> However, in rare cases, higher doses may cause nervous system dysfunction (peripheral neuropathy).<sup>58</sup> Most reported cases of neuropathy associated with vitamin B6 supplementation involved intake of 500 mg or more daily for two years or more.<sup>59</sup> Vitamin B6 doses higher than 100 mg should therefore be used only under medical supervision. The vast majority of people obtain substantial homocysteine-lowering effects with 50-100 mg per day, provided folic acid is at optimal levels.

"Inadequate blood folate is common among those who do not take multivitamin supplements but unusual among those who do."

—Godfrey P. Oakley, MD

US Centers for Disease Control and Prevention

• **Trimethylglycine (TMG).** Also commonly known as betaine, TMG is a constituent of food. The average American ingests 500–2000 mg of TMG a day. Supplemental TMG reduces homocysteine starting at a dose of 1000 mg a day, up to a maximum 20% reduction at 6000 mg per day, the dose often used in severe homocysteine disorders.<sup>60</sup>



TMG is the most effective nutritional agent for suppressing the after-meal surge in homocysteine, slashing levels up to 50%.<sup>60-62</sup> We commonly use 2000 mg per day as a starting dose for fasting homocysteine levels that do not fully respond to the three B vitamins, using higher doses for the after-meal surge seen with methionine loading. Spinach and wheat germ are two particularly rich food sources of TMG. Be aware that the 6000-mg dose of TMG has been found to raise LDL by around 10%,<sup>63</sup> and LDL should therefore be monitored when using this high dose of TMG.

- **Choline.** Choline is directly converted to TMG in the body. Choline is readily available in various foods and also as a nutritional supplement. Most people ingest 300-1000 mg a day from dietary sources. Choline has recently gained acceptance as an essential nutrient. To avoid deficiency states, the National Academy of Sciences and the US Institute of Medicine recommend a daily intake of 550 mg for men and 425 mg for women. Higher doses are required to obtain the full benefit of lowering homocysteine. Like TMG, choline has modest effects on fasting homocysteine and a larger effect on the after-meal surge of homocysteine.<sup>64</sup> A common dose is 2000-4000 mg per day.
- **Avoiding methionine-rich foods.** Methionine is an amino acid found in food, particularly red meats and dairy products. Although methionine is an essential amino acid, it is also suspected to cause atherosclerotic plaque growth, both directly as well as indirectly by increasing homocysteine levels.<sup>65</sup> The US RDA for methionine is 900 mg a day, but the average American takes in a greater quantity of around 2000 mg a day.<sup>37</sup> If excess methionine is available in the diet, more homocysteine is produced. This provides the basis for one of the tests for hidden homocysteine excess, the “methionine-loading” test. The after-meal surge in homocysteine is prevented by vitamin B6 availability, along with choline and TMG.
- **Fish oil.** Along with its other remarkable benefits such as lowering triglycerides, reducing fibrinogen, and stabilizing abnormal heart rhythms, fish oil may lower homocysteine. Homocysteine reductions of 36-48% have been reported,<sup>66,67</sup> though practical experience suggests a more modest drop of 1-2  $\mu\text{mol/L}$  can be expected.
- **Taurine.** This amino acid and byproduct of methionine meta-bolism is emerging as a promising agent for reducing the dangers of homocysteine.<sup>68</sup> However, further human data are needed to assess its effects.
- **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 modest program of regular exercise. How or why exercise results in such a reduction is unclear, but this is yet another example of how physical activity yields broad health-promoting benefits.<sup>69</sup>

## Foods Naturally Rich In Folate

The US government’s mandate to supplement grain products with folic acid means that, in a practical sense, most folic acid-enriched foods (such as white bread, crackers, and breakfast cereals) are highly processed. Substantial quantities of naturally occurring folate are found in several select foods listed below. Spinach, black beans, and wheat germ are the superstars in folic acid content. While it is difficult to obtain sufficient folic acid every day through diet alone, these foods (along with folic acid supplements) can you help meet your requirements.

Keep in mind that the amount of folic acid taken as a supplement is equal to nearly double the amount of food folate. For example, 400 mcg of folate from broccoli yields the same as 200 mcg of a folic acid supplement.<sup>50,58</sup> To avoid confusion, in our list we have converted all units to equivalent quantities of folic acid. It is important to recognize that cooking, canning, and exposing foods for prolonged periods (for example, uncovered in the refrigerator) all sharply diminish the folate content of foods. Recall that the RDA for folic acid is 400 mcg per day. Combining foods rich in folic acid with supplemental folic acid can help you exceed this rock-bottom minimum.

	Folic acid content (mcg)
Avocado: 1 cup, sliced	81
Black beans: 1/2 cup, cooked	128
Broccoli: 1 cup, chopped	55
English walnuts: 1/2 cup, chopped	57
Hazelnuts and filberts: 1/2 cup, whole	65
Orange juice: 6 oz.	54
Romaine lettuce: 1 cup, shredded	64
Spinach: 1 cup, cooked	263

## HOMOCYSTEINE, MOOD, AND MEMORY

Homocysteine plays an important role in depression. Poor response to antidepressant medication, dysthymia (a lesser form of depression), and full-fledged depression have all been linked to low folic acid levels, which are often accompanied by high homocysteine levels.<sup>71</sup> Other studies suggest that higher homocysteine levels are very prevalent among the depressed, with up to 50% of subjects exhibiting homocysteine levels above 10  $\mu\text{mol/L}$ .<sup>72,73</sup>



Antidepressant medications may have limited effectiveness in treating depression, which may, however, respond to folic acid. Studies have firmly established that folic acid replacement, resulting in reduced homocysteine blood levels, is an important treatment for depression. In an Italian study, folic acid supplementation yielded improvements in mood similar to those produced by the use of conventional antidepressants.<sup>74</sup>

Moreover, several studies have shown that response to prescription antidepressants like fluoxetine (Prozac®) is substantially improved by taking as little as 500 mcg of folic acid per day.<sup>75,76</sup> Although few psychiatrists have added folic acid to their antidepressant treatment protocols, the data suggest that this simple, inexpensive treatment should be a part of every depressed person's panel of therapies. Doses of 1000-5000 mcg are most effective, generally along with 25-100 mg of vitamin B6 and 100-500 mcg of vitamin B12.

There is a growing appreciation of the role of folic acid, vitamins B6 and B12, and homocysteine in the cognitive decline associated with aging. It is well established that diminished memory and cognitive function are associated with deficiencies of these B vitamins and higher homocysteine levels.<sup>77,78</sup> An MRI study showed that lower folic acid blood levels were associated with markers of neuropathology in the portion of the brain responsible for higher mental function.<sup>79</sup>

Last year, Italian researchers reported on the relationship between homocysteine, dementia, and Alzheimer's disease. For four years, the investigators followed a group of 816 dementia-free adults, averaging 74 years of age. During this interval, 112 subjects developed dementia, including 70 who were diagnosed with Alzheimer's disease. Individuals who had baseline homocysteine values of greater than 15  $\mu\text{mol/L}$  had a twofold greater risk of developing dementia, and their risk of developing Alzheimer's disease was more than two times higher than in subjects with lower homocysteine values. The scientists concluded that elevated homocysteine is an independent risk factor for developing dementia and Alzheimer's disease.<sup>80</sup>

## HOMOCYSTEINE, BONE DENSITY, AND OSTEOPOROSIS

Homocysteine may play a role in bone density and the risk of osteoporotic fractures, according to emerging findings.<sup>81-83</sup>

Researchers examined the association between homocysteine concentration and the risk of hip fracture in over 2,000 men and women, aged 59-81, enrolled in the Framingham Study.<sup>81</sup> Blood samples from the participants were collected between 1979 and 1982, and were analyzed for homocysteine concentration. The participants were followed through June 1998 for incident hip fracture. Men and women in the highest quartiles of homocysteine concentration experienced a greater risk of hip fracture than those in the lowest quartile—the risk was almost four times higher for men and nearly two times greater for women. The investigators concluded that homocysteine concentration, which can easily be modified with nutritional intervention, is an important risk factor for hip fracture in middle-aged and elderly adults.<sup>81</sup>

## Foods Rich In Choline And Trimethylglycine (Betaine)

Choline and trimethylglycine (TMG) both reduce homocysteine, particularly the surge of homocysteine that occurs after a methionine-rich meal (of meat, for example). Maximum lowering of homocysteine occurs when choline and trimethylglycine are combined with folate-rich foods or folic acid supplements. Below is a list of foods rich in choline or TMG. We confine our list to healthy foods that are rich in these two nutrients and exclude choline- or TMG-rich foods (such as sausage) that are clearly unhealthy for other reasons.

To avoid liver disease from choline deficiency, the US Institute of Medicine recommends a daily choline intake of 550 mg for men and 425 mg for women. The precise dose of choline for lowering homocysteine is not well known, but our clinic has had success with 2000-4000 mg a day. TMG lowers homocysteine starting at a dose of 1000 mg a day, with full effect at 6000 mg per day. As noted previously, high-dose TMG intake may elevate LDL levels, which should be monitored with your doctor's help.<sup>63</sup>



	Choline (mg)	Trimethylglycine (mg)
Almonds: 1/2 cup	37	
Atlantic cod: 4 oz. filet	95	10
Baked beans: 1 cup, canned	80	
Beets: 1 cup, canned and drained	10	466
Broccoli: 2 spears	30	
Brussels sprouts: 1 cup, cooked	64	
Cauliflower: 1 cup, cooked	48	
Chicken: 4 oz. roasted, w/o skin	34	
Green peas: 1 cup	44	
Hazelnuts or filberts: 1/2 cup	31	
Milk: skim, 1 cup	38	4
Oat bran: 1/2 cup, raw	28	15
Orange roughly: 4 oz., cooked	41	
Salmon: 4 oz., cooked	74	
Spinach: 1 cup, raw	180	
Spinach: 1 cup, cooked	45	1,161
Sweet potato: 1 medium	15	39
Tilapia: 4 oz.	94	29
Tofu: 1 cup, soft	69	
Tomatoes: 1 cup, chopped	12	55
Tomato sauce: 8 oz.	50	
Wheat bran: 1/2 cup	37	670
Wheat germ, toasted: 4 tbsp.	38	310
Whole wheat bread: 2 slices	13	101

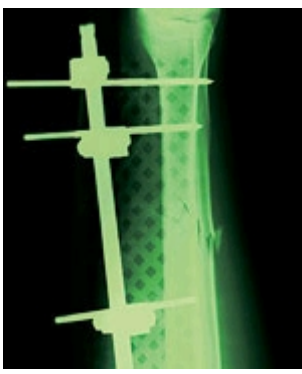
Adapted from the USDA Database for the Choline Content of Common Foods, 2004, and Zeisel et al.<sup>70</sup>

Another study confirmed the relationship between elevated homo-cysteine levels and osteoporotic fractures in older adults. Dutch researchers followed over 2,000 men and women over the age of 55 for five to eight years.<sup>82</sup> They determined that an increased level of homocysteine was a strong risk factor for osteoporotic fracture in both men and women. Their research suggests that the risk posed by elevated homocysteine is independent of other factors such as bone mineral density.<sup>82</sup>

Subsequent research, however, suggests a relationship between homocysteine and bone density. Researchers from Tufts University investigated the relationship between homocysteine, measures of folate and vitamin B12, and bone mineral density in adults aged 55 and older.<sup>83</sup> They found that individuals with serum homocysteine levels equal to or above 20  $\mu\text{mol/L}$  had significantly lower bone mineral density than subjects with homocysteine levels below 10  $\mu\text{mol/L}$ , as determined by DEXA hip scans.

The investigators also found a relationship between bone density and methylmalonic acid, which is a measure of tissue vitamin B12 status. Elevated levels of methylmalonic acid, indicating low tissue levels of vitamin B12, were associated with decreased bone mineral density and an increased prevalence of osteoporosis. The researchers concluded that elevated homocysteine and decreased vitamin B12 status were associated with decreased bone mineral density in older adults. In this study, serum and red blood cell folate levels were not related to bone mineral density or osteoporosis.<sup>83</sup>

In another recent study, the combination of vitamin B12 and folate helped decrease homocysteine levels and prevent hip fractures in individuals who had previously suffered a stroke.<sup>84</sup> Elevated homocysteine is a risk factor for both ischemic stroke and osteoporotic fracture in men and women. Over 500 male and female stroke survivors suffering from residual partial paralysis were supplemented with 5000 mcg of folate and 1500 mcg of vitamin B12 or placebo for two years. At baseline, all the patients had high levels of homocysteine and low serum levels of vitamin B12 and folate. At the two-year follow-up, homocysteine levels increased 31% in the placebo group and fell 38% in the B12-folate group. The B12-folate group also experienced a decreased rate of hip fracture compared to the placebo group. The researchers concluded that supplementing with vitamin B12 and folate is safe and effective in reducing hip fracture risk in elderly patients following a stroke.<sup>84</sup>



Managing elevated homocysteine may thus be an important strategy for preserving bone mineral density, minimizing osteoporosis risk, and preventing bone fractures.<sup>81-84</sup>

While numerous nutritional remedies may be helpful for reducing homocysteine levels, vitamin B12 may play an especially important role in promoting healthy bone mineral density,<sup>83</sup> and the combination of B12 and folate may reduce hip fracture risk following a stroke.<sup>84</sup>

The mechanism by which homocysteine affects bone density and fracture risk remains unknown, but some investigators speculate that high serum homocysteine concentration may weaken bone by interfering with collagen cross-linking, thus increasing the risk of osteoporotic fracture.<sup>81</sup>

Emerging research relates deficient folate and high homocysteine levels with such disparate conditions as complications of pregnancy, inflammatory bowel disease, and some cancers.<sup>85-87</sup> Although we await data demonstrating just how supplementation benefits these conditions, the ease of nutritional intervention argues for simply correcting elevated levels of homocysteine, drawing on the compelling knowledge base already established.

## CONCLUSION

Homocysteine is an amino acid that, even at levels previously regarded as normal, exaggerates the adverse effects of other atherosclerotic risk factors and may heighten long-term risk for heart attack, stroke, osteoporosis, depression, blood clot formation, and even cancer.

Fortunately, the nutritional management of elevated homocysteine levels is a relatively straightforward proposition. Despite the government's well-intended mandate to add folic acid to grain products, most of us are still marginally and sometimes substantially deficient of folic acid. Folic acid supplementation, along with other nutritional strategies to lower homocysteine—using vitamins B6 and B12, choline, and trimethylglycine (TMG)—can provide powerful protection against homocysteine's ill effects on your life and health.

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