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## REPORT

## Battling Heart Disease with B Vitamins

by Angela Pirisi

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Heart disease is the number one killer in North America. Scientists are aggressively seeking to pinpoint the most important risk factors so as to better design a comprehensive preventive strategy against this insidious disease. As it is, heart disease affects 60.8 million Americans and was related to nearly one million deaths in 1998, according to the American Heart Association.

Scientists long ago warned us about the cardiovascular dangers of a high-fat diet, sedentary lifestyle, smoking, high cholesterol-triglycerides and diabetes. In recent years, research has uncovered yet another important culprit in the development of heart disease, namely homocysteine. Study after study over the past decade has shown that, regardless of being clear of other risk factors, even mildly elevated levels of homocysteine in one's bloodstream can single out victims by making them susceptible to heart disease. Homocysteine is a naturally occurring amino acid in the body which, in excessive amounts, tends to build up in the blood and is believed to be at the root of arterial inflammation and damage. What recent research has also turned up is the discovery that folic acid, vitamin B12 and vitamin B6 supplementation can be used successfully to lower homocysteine levels.

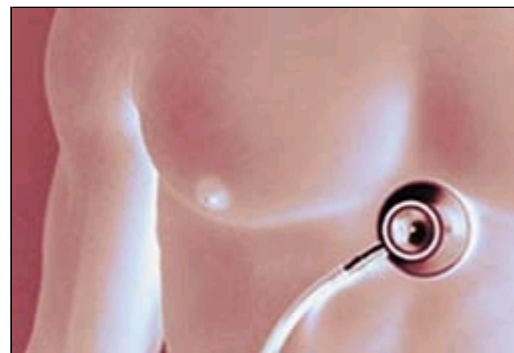
Besides reducing homocysteine concentrations, increasing folic acid, vitamin B6 and B12 intake also works against heart disease by improving vascular endothelial function and related flow-mediated vasodilation.(1-2) A Polish study showed that an eight-week treatment with folic acid (5 milligrams daily), vitamin B6 (300 milligrams daily) and B12 (1000 micrograms weekly) not only cut in half homocysteine levels (from 20 to 10 micromoles/liter). It also diminished the production of a blood-clotting enzyme, thrombin, which plays a proliferative role in heart disease and stroke.(3)

## Nutrient status

As scientists attempted to measure homocysteine levels, they began to look for other markers of high homocysteine levels and their associated cardiovascular (and cerebrovascular) risks. One large focus has been the vital role that certain nutritional deficiencies might play in affecting homocysteine levels and precipitating the arterial damage that leads to cardiovascular disease. So, as much as scientists have devoted time to studying the merits of folic acid and vitamin B12 in reducing the risk of heart disease and stroke, demonstrating the harmful impact of nutritional deficiencies has taught researchers even more about certain vitamins as a preventative means.

For instance, recent studies have noted that suboptimal serum levels of folic acid, vitamin B12 and vitamin B6 may underlie the development of atherosclerosis and coronary heart disease. Why? It's believed that such deficiencies lead to inadequate production of S-adenosyl-methionine, creating a state of turmoil called hypomethylation. And this, in turn, may damage the DNA in arterial cells, leading to the mutation and proliferation of smooth-muscle cells, thus paving the way for atherosclerosis. Many experts believe, however, that vitamin supplementation can not only correct the nutritional deficiencies but also help to reverse the atherosclerotic process in people with existing heart disease.(4)

More specifically, low folate status has been seen as one culprit that precipitates the development of cardiovascular disease. The most recent findings suggest that people with the lowest folate status had more than twice the risk of dying from cardiovascular disease as those with the highest levels of the nutrient. The National Heart, Lung and Blood Institute, Bethesda, MD reported such findings after examining the serum folate concentrations of 689 adults, ages 30 to 75, without cardiovascular disease or diabetes. (5)



Low circulating levels of folate were linked to a 50% greater risk of vascular disease in men. The same study also found that low levels of vitamin B6 increased the risk two to threefold in both sexes.

Similarly, a 15-year Canadian study involving over 5000 men and women with no history of heart disease, aged 35 to 79, showed that the lower the folate levels, the higher was the risk of heart disease-related death. It reported that people with low blood folate levels (below 6.8 nanomoles per liter) have a 69% increase in the risk of fatal coronary heart disease than individuals with higher levels (above 13.6 nanomoles per liter).(6) These study findings are very significant, for one, because the sample included both young and old, male and female. As well, the results point to a correlation between lower blood folate values and mortality, as opposed to just a risk of heart disease, or arterial blockage and damage. What's even more interesting is that the researchers found an inflated risk of death even in people with so-called normal folate status, which calls into question whether we should be boosting our recommended daily allowance. Meanwhile, one multicenter European study, which compared 750 male and female patients with vascular disease to 800 healthy controls, found that low circulating levels of folate were linked to a 50% greater risk of vascular disease in men. The same study also found that low levels of vitamin B6 increased the risk two to threefold in both sexes. (7)

#### How Folic Acid and B12 Reduce Homocysteine

Folic acid and B12 are cofactors of methionine synthase, a key enzyme in homocysteine metabolism.(1) As such, they help to break down the amino acid and convert it into another compound, methionine (which is necessary for proper DNA methylation), indeed pointing to an important pivotal role for these nutrients in heart disease prevention.(2-4) Studies to date have shown that folic acid alone may reduce heart disease risk by as much as 30% to 40%, primarily through its ability to lower homocysteine. In fact, folic acid has been deemed the mainstay of treatment for hyperhomocysteinaemia (elevated homocysteine).(5) However, folic acid works best when teamed up with vitamin B12, which enhances the benefits of folic acid supplementation. (6) Generally speaking, doctors recommend that vitamin B12 be added to supplements containing folic acid, so as to prevent masking of a B12 deficiency.(7)

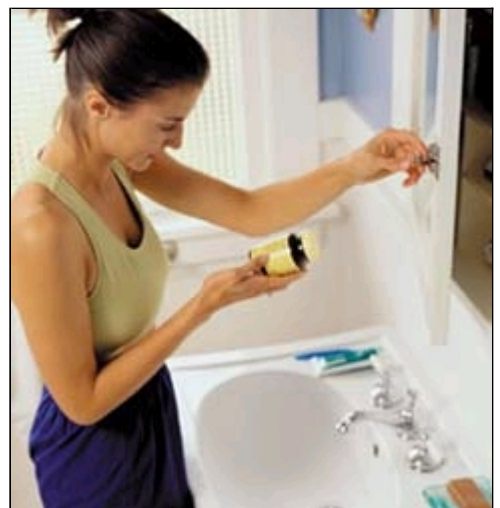
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One study by researchers at the University of Chile even found that, in contrast to other findings, folate levels—and not vitamin B12—were notably low in people with atherosclerosis. The team of scientists had compared serum homocysteine, folate and vitamin B12 measurements among 32 patients with peripheral vascular disease versus 24 healthy controls, and 52 patients with coronary artery disease versus 42 matched controls. Results showed that homocysteine and vitamin B12 levels didn't vary greatly among patients and controls, but that folate levels were 37% lower in vascular patients and 22% lower in coronary patients compared to controls.(8)

A vitamin B12 deficiency has also been noted as contributing to cardiovascular disease. Consider, for instance, evidence from one study conducted in the Slovak Republic that showed that the frequency of high homocysteine levels is higher in vegans (53%) and vegetarians (28%) compared to omnivores (5%).(9) It's believed that the reasons for the huge discrepancies lies in vitamin intake, particularly vitamin B12, as vegans consume none from dietary sources, and vegetarians only consume about one third the amount that omnivores do (124% versus 383% of the RDA). In fact, this study, which examined 62 vegetarians, 32 vegans and 59 omnivores, found that 78% of the vegans studied were vitamin B12-deficient, as were 24% of vegetarians, but 0% of the omnivores showed a deficiency. Folate levels, however, were comparable among the three groups. The authors concluded that vitamin B12 deficiency was chiefly responsible for mildly elevated homocysteine levels in vegans and vegetarians.

Similarly, in many developing countries, studies have found diets low in folate and vitamin B12 are what may account for the increased risk of both cardiovascular disease and neural tube defects. In fact, when US researchers measured the folate and vitamin B12 status of adolescent girls in northern Nigeria of marrying and childbearing age (12 to 16 years), 9% of the subjects had serum vitamin B12 concentrations that fell below the lower limit of the reference range for their age group. This was consistent, said the authors, with the fact that their diet lacks vitamin B12. (10)

Meanwhile, according to a 1998 report by the American Heart Association,(11) about one fifth of the US population may stand a heightened risk of heart attack and stroke because their diet lacks a sufficient amount of vitamin B6 and folic acid. While previous research has suggested that elevated homocysteine levels were the result of too little vitamin B6 or folic acid, the authors of this report were surprised to find that vitamin B6 deficiency was linked to heart disease and stroke risk independently of where homocysteine



Individuals with malabsorption problems, be it from a genetic

levels stood. A B6 deficiency was found among 20% of subjects, and levels of these nutrients were generally lower in individuals with heart disease or stroke than in healthy controls. More importantly, those demonstrating a deficiency had twice the risk of heart disease and stroke. Some research suggests that dietary deficiencies of folic acid, vitamin B12 and vitamin B6 seem common among elderly people in

North America, which might represent “one pathogenic factor related to the incidence of hyperhomocys-teinaemia.”(12) Such deficiencies might also offer a reason why high homocysteine levels seem to prevail among 30% to 40% of the elderly population compared to only 5% to 10% of the general population.(13)

glitch, gastrointestinal diseases, age or existing cardiovascular disease, may need to step up their daily intake through supplementation just to meet the recommended daily allowance.

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### Support for supplementation

Such findings build a strong case for encouraging people to meet their daily requirements of B vitamins. As it stands, though, the average intake among the US adult population is 200 micrograms of folic acid. And food sources, particularly with regards to folic acid, fall short of supplying what the body needs, since only about 50% of it may be bioavailable.(14) As a recent study established, synthetic folic acid from fortified foods or supplements is 1.7 times more bioavailable than food-source folate, which means 100 micrograms of folic acid being equivalent to 170 micrograms of food folate.(15) Moreover, individuals with malabsorption problems, be it from a genetic glitch, gastrointestinal diseases, age or existing cardiovascular disease, may need to step up their daily intake through supplementation just to meet the recommended daily allowance. A researcher at Emory University, Atlanta, GA, Godfrey P. Oakley, Jr., MD, MSPM, even argues that “approximately 70% of the adult population in the United States is exposed to a risk factor for cardiovascular disease—an elevated plasma homocysteine concentration—that can be easily avoided simply by consuming a B vitamin supplement.”(16)

### The need for a higher intake

Of course, some experts argue that the current RDA range may not be high enough to ward off heart disease. Consider that a study review of data and findings from 1966 through 1999 by researchers at Ohio State University reported that studies have demonstrated that using 650 micrograms per day of folic acid brought elevated levels of homocysteine back down to a normal range after just two weeks of treatment.(17) Moreover, when Harvard University researchers tracked more than 80,000 female nurses over a 14-year period, they found that a higher intake of folic acid and vitamin B6 exceeding the recommended daily allowance could help cut the risk of heart disease in half. The female participants were given about 700 micrograms of folate and 4.6 milligrams of B6 per day. The investigative team concluded that it might be prudent to suggest to women that they increase their intake of folate and vitamin B6 above the current recommended dietary allowance for the purpose of staving off heart disease.(18)

Nonetheless, many studies to date do suggest that at the very least we attempt to fulfill the daily requirements as currently approved by the FDA. Two recent studies published in the American Journal of Clinical Nutrition, which examined modifiable lifestyle factors for the prevention of heart disease and stroke, revealed that vitamin supplementation, particularly with folic acid, significantly brought down homocysteine levels. One study consisted of offspring and their spouses aged 28 to 82 years old, of the original Framingham Heart Study, which was initiated in 1950. In this group, significantly lower homocysteine levels were evident in those who regularly took vitamin B supplements, as opposed to those who didn't.(19)

#### B Vitamins' Multiple Benefits

An Australian study suggests that folic acid plays a critical role in heart disease prevention by stopping chromosome breakage and hypomethylation of DNA.(1) Vitamin B12 levels also aid this purpose by facilitating methionine synthase activity, but low vitamin B12 status compromises this important activity. Likewise, folate deficiency causes “expression of chromosomal fragile sites, chromosome breaks, excessive uracil in DNA, micro-nucleus formation and DNA hypomethylation.” The authors suggest, though, that concentrations over and above the current RDIs, meaning more than 200 to 400 micrograms of folic

The second study reported similar findings with regards to moderation and supplementation. Called the New Mexico Aging Process Study, it involved 278 elderly subjects ages 66 to 94. Results from that research, as well as many other studies, show that total folate intake is inversely related to homocysteine concentrations in the blood. More specifically, though, while food folate had a negative dose-response relationship to homocysteine levels, supplements containing folate and vitamin B12 led to levels that were 1.5 micromoles/liter lower than in non-users and independent of food source folate intake.(20)

When folic acid is used in conjunction with vitamins B6 and B12, the results are even more impressive. As a number of studies have demonstrated, treatment with a combination of folic acid, vitamin B6 and vitamin B12 not only reduces plasma homocysteine levels, but also restores endothelial function and undoes arterial plaque.(21) A Canadian double-masked, randomized, multicenter clinical trial, called the Vitamin Intervention for Stroke Prevention (VISP) study is currently underway to assess whether high-dose folic acid, vitamin B6 and vitamin B12 supplementation can aid in the reduction of recurrent stroke compared to a lower intake of these vitamins.

And another study by researchers at the USDA's Human Nutrition Research Center on Aging at Tufts University, Boston, MA, showed that "multivitamin/mineral supplementation can improve B-vitamin status and reduce plasma homocysteine concentration in older adults already consuming a folate-fortified diet."(22) The randomized, double-blind, placebo-controlled trial included 80 men and women aged 50 to 87 with elevated homocysteine (more than or equal to 8 micromoles/liter), who received either a multivitamin & mineral supplement or placebo for eight weeks (56 days) while consuming their usual diet. At follow-up, subjects taking the supplement had significantly higher B-vitamin status and lower homocysteine concentration than controls. Among those who took a daily supplement, plasma folate, pyridoxal phosphate (PLP) and vitamin B12 concentrations rose by 41.6%, 36.5% and 13.8%, respectively, while the average homocysteine concentration decreased by 9.6%. No such positive changes in terms of improved vitamin status and a related drop in homocysteine levels were reported for the placebo group.

What the government recommends is inadequate

The real take-home message from all of these emerging findings is to take stock of your supplement program—it may be the cheapest and simplest strategy in the fight against heart disease and stroke. The quantity of B vitamins needed to fully protect against vascular disease is significantly greater than the government's "Dietary Reference Intakes" (formerly called the Recommended Daily Allowance).

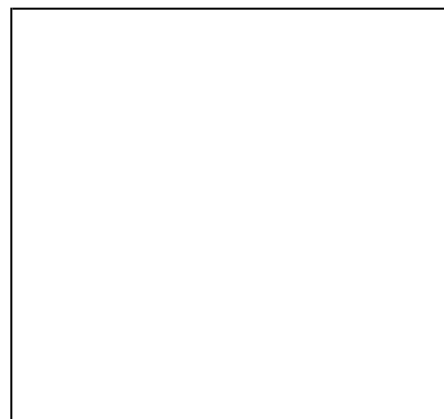
The government, for instance, states that only a few milligrams a day of vitamin B6 are needed to stay healthy, yet to significantly lower homocysteine levels, between 100 and 1000 mg of B6 is often required. The government says only a few micrograms of vitamin B12 are needed to remain alive, yet consuming more than 500 micrograms a day of B12 can greatly assist folic acid in reducing homocysteine concentrations.

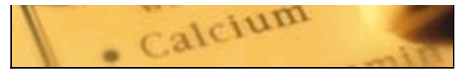
The government states that 200 mcg of folic acid is adequate, yet published studies show that doses of between 400 to 5,000 micrograms of folic acid are optimal for cardiovascular disease risk reduction.

The only way of knowing exactly how many B vitamins you need to reduce your homocysteine to a safe range (below 7 micro mol per liter of blood) is to take a homocysteine blood test. If your homocysteine levels are above 7, despite the vitamin supplement regimen you are following, this means you should consider taking more folic acid, vitamins B12 and B6 and adding trimethylglycine (TMG). The FDA has approved TMG as a drug to lower homocysteine in those who have a genetic defect that causes the excess accumulation of homocysteine. Reducing one's dietary intake of methionine-rich foods such as meat will also facilitate a lower homocysteine level.

acid per day, and more than 2 micrograms vitamin B12 per day, may be crucial for "those with extreme defects in the absorption and metabolism of these vitamins, for which aging is a contributing factor."

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Harvard University researchers tracked more than 80,000 female nurses over a 14-year period. They found that a higher intake of folic acid and vitamin B6 exceeding the recommended daily allowance could help cut the risk of heart disease in half.

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