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REPORT

Preventing Heart Disease and Depression with High-Dose Folic Acid

By Debra Fulghum Bruce, PhD



While modern medicine has succeeded in developing powerful drugs to treat serious diseases, the myriad side effects of these treatments have provoked a renewed interest in preventive medicine. Growing evidence suggests that nutritional therapies can help prevent and manage many lethal diseases, and that their application may lessen the need for more invasive, risky medical interventions.

Folic acid was long ago demonstrated to exert a protective effect against cardiovascular diseases, some forms of cancer, and various neurological impairments. Scientists are now looking at what dose of folic acid might produce optimal effects. Findings from new studies are quite surprising. It turns out that some people may benefit from folic acid doses far exceeding what is found in today's dietary supplements.

WHY WE NEED FOLATE

Folate is necessary for cell replication and growth, as well as the synthesis of DNA and RNA, the cell's genetic blueprints. Folate helps prevent alterations to DNA that can lead to cancer.¹ Both adults and children require folate to build normal red blood cells and prevent one type of anemia.²

Folic acid, also referred to as folate or vitamin B9, has been the subject of growing scientific interest in the past decade. Although not yet widely recognized by the medical community, folic acid may be an important addition to the disease-prevention arsenal, particularly against cardiovascular disease, neuropsychiatric disorders, and certain cancers.

FOLIC ACID AND CARDIOVASCULAR DISEASE

Cardiovascular disease, the number-one killer of men and women, claims the lives of almost 40% of the more than 2.4 million Americans who die each year. Today, about 64 million Americans have some form of cardiovascular disease.³

Homocysteine, a nonessential, sulfur-containing amino acid, is an independent marker of risk for the development of cardiovascular disease, including ischemic heart disease, stroke, and peripheral vascular disease (fatty deposits in the peripheral arteries).⁴ Some researchers consider homocysteine as important a cardiovascular risk factor as low-density lipoprotein (LDL). Homocysteine can make blood clot more easily than normal, increasing the risk of both heart attack and death by heart attack. Inadequate levels of folic acid and vitamins B6 and B12 can lead to increased homocysteine levels.

Studies show that elevated levels of homocysteine may cause endothelial dysfunction of the arteries, an early step in the development of atherosclerosis, the underlying cause of most heart attacks.⁵ The endothelium is the inner layer of cells lining the arteries, and maintaining its integrity is crucial to preventing atherosclerosis. Aging, poor health habits, and biochemical stressors such as elevated homocysteine can weaken the endothelial barrier, allowing blood cells and toxic substances to infiltrate and enter the subendothelial compartment. Lipids such as LDL and triglycerides can accumulate in this area and oxidize. In an attempt to repair the area, smooth muscle cells infiltrate the site, causing an atherosclerotic lesion to form. As this process continues, atherosclerosis progresses, and chronic inflammation takes root in the area. As the body attempts to repair the injured site, calcium accumulation, or hardening of the arteries, can also occur.

In addition to atherosclerosis and thrombosis, endothelial dysfunction and impaired vascular reactivity—possibly representing early large vessel disease—are present in a variety of conditions such as hypertension, diabetes, hyper-cholesterolemia, heart failure, cigarette smoking, hyper-homocysteinemia, and aging.⁵ Infection and the resulting inflammatory response can produce endothelial dysfunction,⁶ as can a brief period of mental stress in healthy young adults with no evidence of vascular disease or risk factors for cardiovascular disease.⁷

In recent years, elevated homocysteine has emerged as an independent risk factor for heart disease.⁸ Overwhelming evidence suggests that folate and homocysteine metabolism are closely linked, and that folic acid supplementation lowers plasma total homocysteine substantially.⁹ Some new findings indicate that lowering homocysteine may improve endothelial function and thus dramatically reduce the risk of cardiovascular disease and heart attack.

THE IMPORTANCE OF SUPPLEMENTING

Undoubtedly, eating folate-rich green leafy vegetables, citrus, nuts, seeds, and meat will boost the body's levels of this B vitamin. However, according to the Institute of Medicine, the body absorbs only about 50% of the folate in food, while absorbing approximately 100% of the folic acid in vitamin supplements.¹⁰

MULTIPLE BENEFITS OF SUPPLEMENTATION

Supplementing with folic acid offers a wealth of benefits. Among other things, folic acid:

- can decrease homocysteinemia, a major risk factor for cardiovascular and other chronic diseases
- can improve endothelial function
- may contribute to the prevention of peripheral artery disease
- may improve lipid profile
- may reverse depression
- can boost the effectiveness of antidepressant therapy
- may help prevent dementia and other neuropsychiatric disorders
- prevents neural tube defects
- appears to reduce the risk of some cancers, such as colon, cervical, and breast cancer
- is safe and inexpensive.

Convinced that folate was crucial in preventing neural tube defects, the Food and Drug Administration in 1998 mandated that manufacturers fortify all cereal grains with folic acid, specifically with a concentration of 140 mcg of folic acid per 100 grams of cereal grain products. This amount provides the average woman with an extra 100 mcg per day of folic acid. While neural tube defects in the US declined significantly after these products were fortified with folic acid, a statistical decline in stroke and ischemic heart disease deaths was also recorded, according to data presented in March 2004 at the American Heart Association's 44th annual Conference on Cardiovascular Disease Epidemiology and Prevention.¹¹

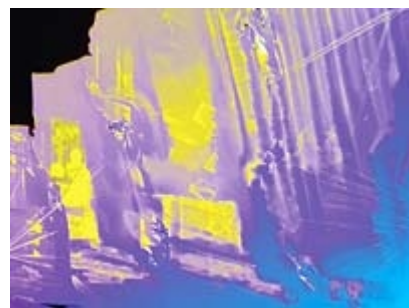
HIGH-DOSE FOLIC ACID AND THE HEART

Around the beginning of the new millennium, Australian researchers speculated that if low-dose folic acid (200 mcg daily) has some therapeutic influence, then higher doses might be even more effective. Investigators from the Institute for International Health at the University of Sydney followed the rationale that lowering homocysteine with folic acid may in turn help reduce the risk of recurrent coronary heart disease. In the PACIFIC Study Group, a trial involving 723 subjects with a history of unstable angina or myocardial infarction, daily doses of both 200 mcg and 2000 mcg of folic acid reduced homocysteine, but the outcome of the higher dose was about one third greater than the lower dose.¹²

Taking the healing potential of folic acid to a new level, investigators at Wales Heart Research Institute in London found that high-dose folic acid (5000 mcg daily) lowered plasma homocysteine by 25% in clinical trials, while improving the bioavailability of nitric oxide.¹³ Nitric oxide is the primary mediator of endothelial function, capable of dilating blood vessels and inhibiting platelet aggregation.

It is common sense that quitting smoking, avoiding saturated and trans fats, and exercising regularly may reduce the risk of cardiovascular disease. For many people, however, these lifestyle changes are not easily attainable. Scientists thus search for any approach that might prevent early endothelial dysfunction and subsequent cardiovascular disease before too much damage occurs.

With this in mind, a team of investigators in Ireland used high-dose folic acid (5000 mcg daily) for four weeks to determine whether supplementation influenced endothelial function in otherwise healthy young cigarette smokers. While measured homocysteine levels stayed about the same in the smokers and the control group, the researchers reported that folic acid supplementation significantly improved endothelial function in healthy young smokers.¹⁴



Photomicrograph of folic acid, essential in the formation of red blood cells. A deficit of folic acid in the diet during the first two weeks of pregnancy causes birth defects such as spina bifida (incomplete development of the vertebral column).



About the same time, re-searchers in the Netherlands examined the effects of folic acid and vitamin B12 in patients with high homocysteine levels and coronary artery disease. Their findings showed that coronary endothelial function improved after just six months of treatment with high-dose folic acid (5000 mcg daily) and vitamin B12 (400 mcg daily).¹⁵

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Researchers at London's Heart and Lung Institute reached the same conclusion: supplementation with folic acid and vitamin B12 improves vascular endothelial function in patients with coronary heart disease.¹⁶ Interestingly, the latest findings from Wales College of Medicine in London show conclusively that lowering homocysteine by methods other than high-dose folic acid—whether using trimethylglycine (TMG), a nutrient used to remove extra homocysteine from the body, or low-dose folic acid—does not improve endothelial function.¹⁷

This raises an obvious question: is supplementing with high-dose folic acid (5000 mcg daily) safe? In an exclusive interview with *Life Extension*, Malcolm J. Lewis, MD, professor of cardiovascular pharmacology and deputy head of the Department of Pharmacology, Therapeutics and Toxicology at Cardiff University, discussed the results of the most recent folic acid trials. Dr. Lewis leads one of the world's premier team of scientists in investigating the role of this B vitamin and its relationship to cardiovascular disease.



Dr. Lewis confirmed the safety and effectiveness of high-dose folic acid, saying that findings reported at the May 2004 meeting of the British Cardiac Society “clearly demonstrated that although both 400 mcg and [5000 mcg] of folic acid can lower homocysteine levels to the same extent in patients with coronary disease, only the [5000- mcg daily dose] was effective at improving endothelial function (an excellent surrogate for cardiovascular health). None of the subjects in any of our studies has had adverse effects from taking [5000 mcg] of folic acid. Provided vitamin B12 deficiency has been excluded, this dose would seem safe to use.”¹⁸

Dr. Lewis added, “It is obvious, therefore, that ‘high’ doses of folate have pharmacological effects which are different from more conventionally used ‘low’ doses. We are currently investigating why this may be the case.”¹⁸

Some new studies speculate that folic acid's ability to reverse endothelial dysfunction is independent of its ability to lower plasma homocysteine levels. Lewis and his team recently reported that reversing endothelial dysfunction with folic acid shows that this B vitamin has myriad effects on the vasculature besides lowering homocysteine. In-vitro evidence demonstrates that 5-methyltetrahydrofolate, the main circulating metabolite of folic acid, can increase nitric oxide production and directly scavenge superoxide radicals. These properties may account for some of its cardioprotective effects.¹⁹

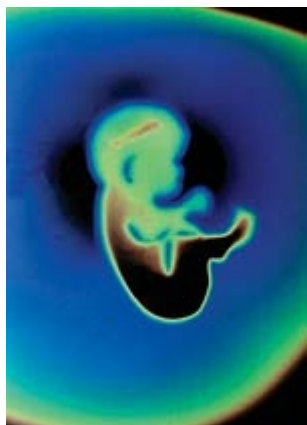
WOMEN AND HEART DISEASE

Heart disease was once believed to be a man's disease. Before the age of 60, men die of heart attack at six times the rate that women do. By the age of 70, however, heart attack rates for men and women are virtually even. Doctors now confirm that heart disease is so deadly for women that they have a 50% chance of dying from it. And the younger a woman is, the less likely she is to have symptoms of heart disease.³⁵

After menopause, which signifies the end of a woman's reproductive years, many women gain weight. As levels of the hormone estrogen decline, blood pressure increases. Studies show that many postmenopausal women have higher levels of triglycerides, total cholesterol, and low-density lipoprotein (LDL) than premenopausal women.³⁶ Realizing the impact of menopause and declining estrogen on women's heart health, researchers at the Catholic University of Sacred Heart in Rome, Italy, sought to determine whether folic acid supplementation affected endothelial function in 15 healthy postmenopausal women.

Published in 2004, this groundbreaking study measured the women's plasma levels of folate, homocysteine, glucose, insulin, and lipids, as well as their blood pressure. After just one month of supplementation with high-dose folic acid (7500 mcg daily), the women's endothelial function improved 37% compared to pre-supplementation values. Among the other cardiovascular risk factors studied, beneficial high-density lipoprotein (HDL) levels increased 6%, while dangerous low-density lipoprotein (LDL) dropped 9%. These findings further substantiate that high-dose folic acid supplementation may improve endothelial function and lipid profile to reduce cardiovascular disease risk.³⁷

Researchers now believe that major depressive disorders and cardiovascular disease are mutually associated, sharing signs and symptoms of metabolic syndrome, usually caused by being overweight or obese, lack of physical exercise, and genetic factors (see "Heart and Mind: The Dangerous Link Between Heart Disease and Depression," *Life Extension*, January 2005). Scientists in the Netherlands recently observed that in both major depressive disorders and cardiovascular disease, omega-3 polyunsaturated fatty acids are diminished while plasma homocysteine levels are elevated.²⁰ While most folic acid studies have focused on heart health, some recent findings suggest that folic acid either has antidepressant properties or can act as an augmenting mediator for standard antidepressant treatment.



Although the link between folate deficiency and neuropsychiatric disorders is not well understood, several subjective cases have established an intriguing relationship. Dr. Victor Herbert, the late hematologist and nutritional scientist, experimented on himself 40 years ago to better understand folate deficiency, eating foods thrice boiled to extract folate.²¹ In the state of induced folate deficiency from diet restriction, Herbert noted that central nervous system effects, including irritability, poor memory, and increasing sleeplessness, appeared within four to five months. Interestingly, Herbert reported that all central nervous system symptoms disappeared within 48 hours after taking oral folate.²² (Victor Herbert, MD, died in 2002 at the age of 75. According to his family, the cause of death was melanocytoma, "a rare form of neurological cancer."²³)

HOW DOES IT WORK?

In the body, folate is crucial to the production of S-adenosyl-L-methionine (SAMe), the methyl-group donor involved in the biosynthesis of DNA, RNA, phospholipids, proteins, and other molecules.

SAMe is also involved in the synthesis of catecholamine neurotransmitters, such as epi-nephrine, that appear to play a role in determining mood.²⁴ Depressive symptoms are the most common neuropsychiatric manifestation of folate deficiency. Borderline low or deficient serum or red blood cell folate levels are seen in 15-38% of adults diagnosed with depressive disorders.²⁵ Doctors now believe that patients with low plasma folate levels do not respond to antidepressant treatment as well as those with adequate folate levels.²⁵ Consequently, folate is believed to play an important role in regulating mood.

According to a report published in 2003, some people with depression appear to have problems metabolizing folate. This is consistent with the idea that folic acid supplements might help reverse or even prevent depression. In this study of 5,948 people aged 46 to 49, Norwegian scientists found that people with high blood levels of homocysteine were almost twice as likely to be depressed as those with normal levels.²⁶

Scientists from Finland have continued to unravel the connection between folate and depression. Analyzing the diets of 2,682 men aged 42 to 60, they found that men with the lowest dietary folate intake had a 67% greater risk of having elevated depressive symptoms than those with the highest intake. The authors concluded that nutrition may play an important role in mental health and in preventing depression.²⁷

FOLIC ACID AND ANTIDEPRESSANTS

In a study of patients previously unresponsive to selective serotonin re-uptake inhibitors (SSRIs), folic acid boosted the response rate, even in those who had normal folate levels at the trial's onset.²⁸ Emerging evidence from randomized trials shows that the combination of folate and conventional antidepressant treatments may improve outcomes.²⁹ In a study published last year, Harvard researchers noted that depressed people with low serum folate levels had poorer responses to antidepressant therapy.³⁰ Evidence suggests that elderly depressed patients have lower levels of folate than their non-depressed cohorts. Supplementing with folate may thus reduce the incidence of depression in the elderly.³¹

THE ALZHEIMER'S CONNECTION

A study published in the *New England Journal of Medicine* in 2002 reported that people with high blood levels of homocysteine (greater than 14 mmol/L) have twice the normal risk of developing Alzheimer's disease.³² Alzheimer's destroys brain cells and the important neurotransmitter acetylcholine, the chemical messenger responsible for memory and other cognitive skills. High homocysteine levels have also been associated with impairment in verbal memory, fine motor skills, and cognition,³³ as well as with stroke.³⁴

Low folate levels are associated with increased levels of homocysteine. With research still in the early stages, scientists theorize

THE FOLIC ACID-VITAMIN B12 CONNECTION

When taking 5000 mcg of folic acid daily, it is important to note that this high dose may mask a diagnosis of pernicious anemia due to vitamin B12 (cobalamin) deficiency, and may even enhance the severity of neuropsychiatric complications.³⁸

Animal products such as meat and dairy foods are the only dietary sources of vitamin B12 for humans. Those most prone to vitamin B12 deficiency are people with little dietary variation (including vegetarians and vegans), alcoholics, those who take certain medications, and the elderly. To eliminate the danger of irreversible nerve damage, simply take vitamin B12, which is included in most multi-vitamin supplements, in combination with folic acid.

that high homocysteine levels may cause brain injury and neuropsychiatric disorders. Increased intake of folic acid and other B vitamins may help to prevent cognitive impairment, dementia, and Alzheimer's disease in people with elevated homocysteine levels.



CONCLUSION

High-dose folic acid—up to 5000 mcg daily—is a scientifically substantiated and safe nutritional approach to achieving optimal health in men and women who want to prevent or reverse chronic illness. With demonstrated benefits in reducing cardiovascular risk factors, preventing and enhancing treatment outcomes in depression, and preventing cancer, folic acid is highly indicated as a therapeutic ally for men and women of all ages. The US recommended dietary allowance (RDA) of 400 mcg of folic acid, established by the National Academy of Sciences and National Research Council, is the minimal amount necessary to prevent gross deficiency syndromes. This nominal level is not at all adequate for preventing

chronic disease.

Much remains unknown about chronic and degenerative ailments such as cardiovascular disease and neuropsychiatric disorders. Ground-breaking findings continue to be published. Only in the past decade have scientists begun to unravel how nutrients help the human body prevent, manage, and treat disease. Inexpensive and readily available to most people, high-dose folic acid has the potential to positively influence the health of people throughout the world.

FOLIC ACID AND CANCER

Folate deficiency may contribute to abnormal DNA synthesis and carcinogenesis by interfering with normal DNA methylation. In recent years, increasing evidence indicates that folic acid plays a role in preventing certain cancers.³⁸

Data suggest that low levels of folic acid may result in increased rates of cervical and colorectal cancer. In the Nurses' Health Study, which followed more than 121,000 nurses aged 30 to 55 during an 18-year period from 1976 to 1994, Harvard researchers concluded that women with a high folic acid intake were 75% less likely to develop colon cancer than those with a lower intake.³⁹ Other studies have reported strong links between low levels of folic acid and cancers of the breast, lung, esophagus, and stomach.

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