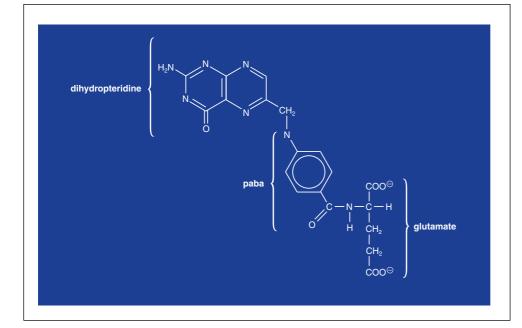# Folic Acid

Introduction

Folic acid, also known generically as folate or folacin, is a member of the B-complex family of vitamins, and works in concert with vitamin B12. Folic acid functions primarily as a methyl-group donor involved in many important body processes, including DNA synthesis. Therapeutically, folic acid is instrumental in reducing homocysteine levels and the occurrence of neural tube defects. It may play a key role in preventing cervical dysplasia and protecting against neoplasia in ulcerative colitis. Folic acid also shows promise as part of a nutritional protocol to treat vitiligo, and may reduce inflammation of the gingiva. Furthermore, certain neurological, cognitive, and psychiatric presentations may be secondary to folate deficiency. Such presentations include peripheral neuropathy, myelopathy, restless legs syndrome, insomnia, dementia, forgetfulness, irritability, endogenous depression, organic psychosis, and schizophrenia-like syndromes.

Biochemistry

Folic acid is a water-soluble member of the B-complex family of vitamins. Folic acid is composed of three primary structures, a hetero-bicyclic pteridine ring, para-aminobenzoic acid (PABA), and glutamic acid. Because humans cannot synthesize this compound, it is a dietary requirement.

Although folic acid is the primary form of folate used in dietary supplements or fortified foods, it comprises only 10 percent or less of folates in the diet. Dietary folic acid, or the form naturally found in foods, is actually a complex and variable mixture of folate compounds, such as polyglutamate (multiple glutamate molecules attached) conjugate compounds, reduced folates, and tetrahydrofolates. Although folates are abundant in the diet, cooking or processing destroys these compounds. The best folate sources in foods are green, leafy vegetables; sprouts, fruits, brewer's yeast, liver, and kidney also contain high amounts of folates.

Pharmacokinetics

Human pharmacokinetic studies indicate folic acid has very high bioavailability, with large oral doses of folic acid substantially raising plasma levels in healthy subjects in a time- and dose-dependent manner. Subsequent to high-dose oral administration of folic acid (ranging from 25-1,000 mg/day), red blood cell (RBC) folate levels remain elevated for periods in excess of 40 days following discontinuation of the supplement. Folic acid is poorly transported to the brain and rapidly cleared from the central nervous system. The primary methods of elimination of absorbed folic acid are fecal (through bile) and urinary.[1-4]

After ingestion, the process of conversion of folic acid to the metabolically active coenzyme forms is relatively complex. Synthesis of the active forms of folic acid requires several enzymes, adequate liver and intestinal function, and adequate supplies of riboflavin (B2), niacin (B3), pyridoxine (B6), zinc, vitamin C, and serine. After the formation of the coenzyme forms of the vitamin in the liver, these metabolically active compounds are secreted into the small intestine with bile (the folate enterohepatic cycle), where they are reabsorbed and distributed to tissues throughout the body. Despite the biochemical complexity of this process, evidence suggests oral supplementation with folic acid is able to increase the body's pool of the active reduced folate metabolites (such as methyltetrahydrofolate) in healthy individuals.[5]

Enzyme defects, malabsorption or digestive system pathology, and liver disease can result in impaired ability to activate folic acid to the required coenzyme forms in the body. Evidence indicates some individuals have a severe congenital deficiency of the enzyme methyltetrahydrofolate reductase, which is needed to convert folic acid to the 5-methyltetrahydrofolate coenzyme form of the vitamin. The existence of milder forms of this enzyme defect is strongly suspected and likely interacts with dietary folate status to determine risk for some disease conditions.[6-10] In individuals with a genetic defect of this enzyme (whether mild or severe), greater dietary exposure to foods rich in folates and supplemental folates in the form of folinic acid or 5-methyltetrahydrofolate might be preferable to folic acid supplementation.

Mechanisms of Action

Folic acid's primary mechanisms of action are through its role as a methyl donor in a range of metabolic and nervous system biochemical processes, as well as being necessary for DNA synthesis. Serine reacts with tetrahydrofolate, forming 5,10-methylenetetrahydrofolate, the folate derivative involved in DNA synthesis. A methyl group is donated to cobalamin (B12) by 5-methyltetrahydrofolate, forming methylcobalamin. With the help of the enzyme methionine synthase, methylcobalamin donates a methyl group to the amino acid metabolite homocysteine, converting it to the amino acid methionine.

Methionine subsequently is converted to S-adenosylmethionine (SAMe), a methyl donor involved in numerous biochemical processes.

Deficiency States and Symptoms

Folic acid deficiency is considered to be one of the most common nutritional deficiencies. The following may contribute to a deficiency of folic acid: deficient food supply; defects in utilization, as in alcoholics or individuals with liver disease; malabsorption; increased needs in pregnant women, nursing mothers, and cancer patients; metabolic interference by drugs; folate losses in hemodialysis; and deficiencies in enzymes or cofactors needed for the generation of active folic acid.[11] Absorption of folic acid appears to be significantly impaired in HIV disease, irrespective of the stage of the disease.[12]

Signs and symptoms of folate deficiency include macrocytic anemia, fatigue, irritability, peripheral neuropathy, tendon hyper-reflexivity, restless legs syndrome, diarrhea, weight loss, insomnia, depression, dementia, cognitive disturbances, and psychiatric disorders.[13-18] Elevated plasma homocysteine can also indicate a dietary or functional deficiency of folic acid.

Clinical Indications
Anemia

Folic acid has a long history of use in conjunction with vitamin B12 for the treatment of macrocytic anemia. Depending on the clinical status of the patient, the dose of folic acid required to reverse macrocytic anemia varies, but the therapeutic dose is usually 1 mg daily. Duration of therapy to reverse macrocytic anemia can be as short as 15 days after initiation of supplementation, or it may require prolonged supplementation.

Cervical Dysplasia

Research points to an association between folate status in adults and cervical dysplasia;[19-21] however, its role as an efficacious therapeutic intervention is unclear. One report suggests folic acid supplementation (10 mg folic acid for three months) reverses cervical dysplasia in women taking oral contraceptives.[22] In another study, 154 individuals with grade 1

or 2 cervical intraepithelial neoplasia were randomly assigned either 10 mg folic acid or placebo daily for six months. No significant differences were observed between supplemented and unsupplemented subjects regarding dysplasia status, biopsy results, or prevalence of human papilloma virus type-16 infection.[23] It is possible certain subsets of women (perhaps those with an oral contraceptive-induced deficiency) might be more amenable to treatment; however, additional research is required to clarify the therapeutic role of folic acid in cervical dysplasia.

Gout

There is no evidence demonstrating efficacy of folic acid supplementation in gout. Although some *in vitro* evidence suggests folate compounds are potent inhibitors of xanthine oxidase activity,[24] it appears pterin aldehyde, a photolytic breakdown product of folic acid, and not folic acid itself, is responsible for the observed inactivation of xanthine oxidase.[25]

Available evidence has shown no ability of supplemental folic acid in oral daily doses up to 1,000 mg to significantly lower serum urate concentration, or to decrease urinary urate or total oxypurine excretion in hyperuricemic subjects.[26]

Homocysteinemia

An abnormally high plasma level of homocysteine, the de-methylated derivative of the amino acid methionine, is an independent risk factor for cardiovascular disease. Elevated plasma homocysteine has been connected to increased risk of neural tube defects and other birth defects, as well as to schizophrenia, Alzheimer's disease, cognitive decline, osteoporosis, rheumatoid arthritis, kidney failure, and cancer.[27-31]

The activated coenzyme form of folic acid (5-methyltetrahydrofolate) is needed for optimal homocysteine metabolism, since it acts as a methyl donor, providing a methyl group to vitamin B12. The methylated form of vitamin B12 (methylcobalamin) subsequently transfers this methyl group to homocysteine. The result is a recycling of homocysteine to methionine, resulting in reduction in elevated plasma homocysteine.

In healthy subjects even low doses of folic acid can lower homocysteine levels. A dose of 250 mcg daily for four weeks reduced homocysteine an average of 11.4 percent in healthy 18- to 40-year-old women. A dose of 500 mcg daily for the same duration reduced levels an average of 22 percent.[32] In a separate study, 650 mcg daily for six weeks resulted in an average plasma homocysteine reduction of 41.7 percent.[33]

In subjects with cardiovascular disease, 800 mcg folic acid daily resulted in an average decrease in homocysteine levels of 23 percent,[27] while 2.5 mg daily resulted in an average decrease of 27 percent.[34] In subjects receiving the higher dose, 94 percent experienced some degree of reduction in homocysteine.[28] Evidence suggests individuals with higher initial homocysteine levels are likely to experience a greater reduction following folic acid supplementation.[34]

In addition to helping reduce blood levels of homocysteine, folic acid may also aid peripheral blood flow by increasing nitric oxide (NO) in vascular endothelial cells. Impaired endothelial NO activity is an early marker for cardiovascular disease, particularly atherosclerosis. In fact, most of the risk factors for atherosclerosis are associated with poor vasodilation due to insufficient NO production. Chronic, unopposed exposure of the vascular endothelium to homocysteine compromises the production of adequate amounts of NO, which leads to injury of the endothelial lining and the initiation/exacerbation of atherosclerosis and/or thrombus formation. Folic acid appears to improve NO synthesis by reducing plasma homocysteine levels, enhancing the availability of key endothelial NO cofactors, and reducing the production of superoxide anions, the net effect of which is improvement of peripheral blood flow.[35,36]

In a recent doubled-blind, placebo-controlled, crossover study of individuals with coronary heart disease, researchers found supplementation with high-dose folic acid (30 mg per day) improved blood flow to the heart muscle via the coronary arteries. Using positron emission tomography (PET scanning), researchers at Massachusetts General Hospital noted significant improvement in coronary blood flow with folic acid supplementation compared to placebo. The improvement was especially enhanced in areas of the heart that had shown reduced blood flow prior to supplementation. Folic acid supplementation also significantly lowered the study participants' blood

pressure. The findings from this high-dose folate study demonstrate another significant way this nutrient benefits the cardiovascular system.[37]

Although excellent results have been achieved with folic acid monotherapy, available evidence suggests an additive effect exists between folic acid and vitamins B6, B12, and betaine with respect to lowering homocysteine levels. Combinations of these nutrients typically produce greater reductions in homocysteine than does folic acid alone.[27-29,38] Furthermore, the addition of vitamin C, L-arginine, tetrahydrobiopterin (BH_4), and polyunsaturated fatty acids (PUFAs) has been suggested as a means of enhancing the effect of folic acid on endothelial NO production.[35]

Inflammatory Bowel Disease

Patients with inflammatory bowel disease (IBD) often have folate deficiencies, caused in part by the drug sulfasalazine, prescribed for IBD but also known to inhibit folate absorption.[39] Evidence suggests folic acid supplementation might lower the risk, in a dose-dependent fashion, of colonic neoplasia in patients with ulcerative colitis. A review of 99 ulcerative colitis (UC) patient records found folic acid supplementation was associated with a 62-percent decreased risk of neoplasia compared to patients not taking folate supplements.[39] In another similar study, the files of 98 UC patients disclosed dose-dependent protection from neoplasia by folic acid. The relative risk of developing neoplasia was 0.76 for 400 mcg folate and 0.54 for those taking 1 mg folate for at least six months compared to those not supplemented.[40]

Neuropsychiatric Applications

Neuropsychiatric diseases encompass a number of neurological, cognitive, and psychiatric presentations that may be secondary to folate deficiency. Such presentations include dementia, schizophrenia-like syndromes, insomnia, irritability, forgetfulness, endogenous depression, organic psychosis, peripheral neuropathy, myelopathy, and restless legs syndrome.[14-18]

Lower serum and RBC folate concentrations have an association with depression, and deficiency might predict a poorer response to some antidepressant medications.[30,41-47] Several studies have documented improvement in depression in some patients

subsequent to oral supplementation with the coenzyme form of folic acid (methyltetrahydrofolate) at doses of 15-50 mg daily.[48,49] Folic acid (500 mcg per day) significantly improved the antidepressant action of fluoxetine in subjects with major depression.[50]

Limited evidence implies supplemental folic acid might positively affect morbidity of some bipolar patients placed on lithium therapy.[51]

A syndrome characterized by mild depression, permanent muscular and intellectual fatigue, mild symptoms of restless legs, depressed ankle jerk reflexes, diminution of vibration sensation in the legs, stocking-type hypoesthesia, and long-lasting constipation appears to respond to folic acid supplementation (5-10 mg per day for 6-12 months).[52]

Periodontal Disease

Folic acid can increase the resistance of the gingiva to local irritants and lead to a reduction in inflammation. A mouthwash containing 5 mg folate per 5 mL of mouthwash used twice daily for four weeks, with a rinsing time of one minute, appears to be the most effective manner of application. The effect of folate on gingival health appears to be moderated largely, if not totally, through a local influence.[53-54]

Pregnancy

Low dietary intake of folic acid increases the risk for delivery of a child with a neural tube defect (NTD). Periconceptional folic acid supplementation significantly reduces the occurrence of NTD.[56-62]

Supplemental folic acid intake during pregnancy results in increased infant birth weight and improved Apgar scores, along with a concomitant decreased incidence of fetal growth retardation and maternal infections.[63-65]

Vitiligo

In some individuals, administration of folic acid appears to be a rational aspect of a nutritional protocol to treat vitiligo. Degrees of re-pigmentation ranging from complete re-pigmentation in six subjects and 80-percent re-pigmentation in two subjects were reported in eight individuals who followed a three-year protocol with a dosage of 2 mg folic acid twice daily, 500 mg vitamin C twice daily, and intramuscular injections of vitamin B12 every two weeks.[66]

A two-year study using a combination of folic acid, vitamin B12, and sun exposure for treatment of vitiligo reported positive results. One hundred patients with vitiligo were treated, with re-pigmentation occurring in 52 subjects. Total re-pigmentation was seen in six patients and the spread of vitiligo was halted in 64 percent of the patients. Re-pigmentation was most evident on sun-exposed areas.[67]

Drug-Nutrient Interactions

A number of drugs can interfere with the pharmacokinetics of folic acid.

Cimetidine and antacids appear to reduce folate absorption.[68]

Sulfasalazine interferes with folic acid absorption and conversion to the active form.[69] Supplementation with folic acid (15 mg/day for one month) prevents folate deficiency in patients with inflammatory bowel disease treated with sulfasalazine.[70]

Continuous long-term use of acetaminophen and aspirin, ibuprofen, and other non-steroidal anti-inflammatory drugs appears to increase the body's need for folic acid.[69]

Although the mechanism is unclear, anticonvulsants, antituberculosis drugs, alcohol, and oral contraceptives produce low serum and tissue concentrations of folate.[69,71]

Folic acid reduces elevated liver enzymes induced by methotrexate therapy in rheumatoid arthritis; however, it had no effect on the incidence, severity, and duration of other adverse events.[72]

Folic acid supplementation prevents nitric oxide synthase dysfunction induced by continuous nitroglycerin use.[73]

Anti-seizure medications, including carbamazepine and phenobarbital, appear to utilize folic acid during hepatic metabolism. Folic acid supplementation can increase metabolism of these drugs, thus lowering blood levels of the drugs and possibly resulting in breakthrough seizures. Initiating folic acid therapy after starting these drugs in individuals should be done with caution.[74]

The anticonvulsant drugs phenytoin and valproic acid appear to interfere with folate absorption.[75] Folic acid supplementation, at a time of day other than when taking an anticonvulsant, may be helpful to prevent deficiency.

There is conflicting information regarding the effects of folate supplementation in individuals treated with antifolate medications such as methotrexate (MTX) and 5-fluorouracil (5-FU). There is evidence folic acid might inhibit the activity of these drugs, although in some cases it may increase activity. In fact, the folic acid metabolite, folinic acid (also known as 5-formyltetrahydrofolate and leucovorin), is often used to "rescue" normal tissue after MTX or 5-FU therapy. Folic acid supplementation does not appear to interfere with methotrexate's anti-arthritic or anti-inflammatory activity. Since these medications are used to treat a wide range of malignant and nonmalignant disorders, indiscriminate use of folates should be avoided until further investigation is conducted.

Nutrient-Nutrient Interactions

Some concern exists that supplementation with high doses of folic acid could mask a vitamin B12 deficiency, resulting in neurological injury secondary to undiagnosed pernicious anemia. If there is any possibility of B12-induced anemia in an individual needing folate therapy, dual therapy with B12 and folate should be administered.

Some authors have suggested folic acid supplements might interfere with intestinal zinc absorption; however, doses as high as 15 mg folic acid daily do not appear to have any significant effect on zinc status in healthy, non-pregnant subjects.[74]

Side Effects and Toxicity

In doses typically administered for therapeutic purposes, folic acid is considered non-toxic. At doses of 15 mg daily and above, gastrointestinal complaints, insomnia, irritability, and fatigue have been mentioned as occasional side effects.

Folic acid is considered safe during pregnancy, with an established recommended intake of 800 mcg daily.

Dosage

The dose of folic acid required varies depending on the clinical condition. For lowering homocysteine, a minimum dose of 800 mcg daily is generally used. The most common therapeutic dose is in the range of 1-3 mg daily. Doses greater than 10 mg daily have been used in conditions such as cervical dysplasia.

Dosages of over-the-counter folic acid supplements are restricted to no more than 800 mcg of folic acid per serving, although prescription forms of folic acid are available in higher doses.

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