Biotin

Biotin is a water-soluble vitamin that is generally classified as a B-complex vitamin. After the initial discovery of biotin, nearly 40 years of research were required to establish it as a vitamin (1). Biotin is required by all organisms but can be synthesized only by bacteria, yeasts, molds, algae, and some plant species (2).

Function

Biotin is attached at the active site of five mammalian enzymes known as carboxylases (3). The attachment of biotin to another molecule, such as a protein, is known as "biotinylation." Holocarboxylase synthetase (HCS) catalyzes the biotinylation of apocarboxylases (i.e., the catalytically inactive form of the enzyme) and of histones (See below). Biotinidase catalyzes the release of biotin from histones and from the peptide products of carboxylase breakdown.

Enzyme cofactor

Each carboxylase catalyzes an essential metabolic reaction:

- **Acetyl-CoA carboxylase I and II** catalyze the binding of bicarbonate to acetyl-CoA to form malonyl-CoA. Malonyl-CoA is required for the synthesis of fatty acids. The former is crucial in cytosolic fatty acid synthesis, and the latter functions in regulating mitochondrial fatty acid oxidation.
- **Pyruvate carboxylase** is a critical enzyme in gluconeogenesis—the formation of glucose from sources other than carbohydrates, for example, amino acids.
- **Methylcrotonyl-CoA carboxylase** catalyzes an essential step in the catabolism of leucine, an essential amino acid.
- **Propionyl-CoA carboxylase** catalyzes essential steps in the metabolism of certain amino acids, cholesterol, and odd chain fatty acids (fatty acids with an odd number of carbon molecules) (4).

Histone biotinylation

Histones are proteins that bind to DNA and package it into compact structures to form nucleosomes—integral structural components of chromosomes. The compact packaging of DNA must be relaxed somewhat for DNA replication and transcription to occur. Modification of histones through the attachment of acetyl or methyl groups (acylation or methylation) has been shown to affect the structure of histones, thereby affecting replication and transcription of DNA. Mounting evidence indicates that biotinylation of histones plays a role in regulating DNA replication and transcription as well as cellular proliferation and other cellular responses (5-7).

Deficiency

Although overt biotin deficiency is very rare, the human requirement for dietary biotin has been demonstrated in two different situations: prolonged intravenous feeding (parenteral) without biotin supplementation and consumption of raw egg white for a prolonged period (many weeks to years). Avidin is an antimicrobial protein
found in egg white that binds biotin and prevents its absorption. Cooking egg white denatures avidin, rendering it susceptible to digestion and therefore unable to prevent the absorption of dietary biotin (8).

Three measures of biotin status have been validated as indicators of biotin status: (1) high excretion of an organic acid (3-hydroxyisovaleric acid) that reflects decreased activity of the biotin-dependent enzyme, methylcrotonyl-CoA carboxylase; (2) reduced urinary excretion of biotin; and (3) propionyl-CoA carboxylase activity in peripheral blood lymphocytes (4, 9-11).

**Signs and symptoms**

Signs of overt biotin deficiency include hair loss and a scaly red rash around the eyes, nose, mouth, and genital area. Neurologic symptoms in adults have included depression, lethargy, hallucination, and numbness and tingling of the extremities. The characteristic facial rash, together with unusual facial fat distribution, has been termed the "biotin deficient facies" by some investigators (8). Individuals with hereditary disorders of biotin metabolism resulting in functional biotin deficiency often have similar physical findings as well as evidence of impaired immune system function and increased susceptibility to bacterial and fungal infections (12).

**Predisposing conditions**

There are several ways in which the hereditary disorder, biotinidase deficiency, leads to biotin deficiency. Intestinal absorption is decreased because a lack of biotinidase inhibits the release of biotin from dietary protein. Recycling of one's own biotin bound to protein is impaired, and urinary loss of biotin is increased because the kidneys more rapidly excrete biotin that is not bound to biotinidase (5, 8). Biotinidase deficiency uniformly responds to moderate biotin supplementation. Oral supplementation with as much as 5 to 10 milligrams (mg) of biotin daily is sometimes required, although smaller doses are often sufficient. Some forms of holocarboxylase synthetase (HCS) deficiency respond to biotin supplementation with large doses. HCS deficiency results in an enzyme that catalyzes the attachment of biotin to all four carboxylase enzymes (see **Function**). HCS deficiency results in decreased formation of all holocarboxylases at normal blood levels of biotin; thus, high-dose supplementation (40 mg to 100 mg of biotin/day) is required. The inborn error, biotin transporter deficiency, also responds to high-dose biotin supplementation (13). The prognosis of all three of these disorders is often, but not always, good if biotin therapy is introduced early (infancy or childhood) and continued for life (12).

Aside from prolonged consumption of raw egg white or total intravenous nutritional support lacking biotin, other conditions may increase the risk of biotin depletion. The rapidly dividing cells of the developing fetus require biotin for histone biotinylation and synthesis of essential carboxylases; hence, the biotin requirement is likely increased during pregnancy. Research suggests that a substantial number of women develop marginal or subclinical biotin deficiency during normal pregnancy (6, 14). However, the recommended adequate intake does not change for pregnancy (See **below**). Additionally, some types of liver disease may decrease biotinidase activity and theoretically increase the requirement for biotin. A study of 62 children with chronic liver disease and 27 healthy controls found serum biotinidase activity to be abnormally low in those with severely impaired liver function due to cirrhosis (15). However, this study did not provide evidence of biotin deficiency. Further, anticonvulsant medications, used to prevent seizures in individuals with epilepsy, increase the risk of biotin depletion (16, 17). See **Safety** for more information on biotin and anticonvulsants.
The Adequate Intake (AI)

In 1998, the Food and Nutrition Board of the Institute of Medicine felt the existing scientific evidence was insufficient to calculate a RDA for biotin, so they set an Adequate Intake level (AI). The AI for biotin assumes that current average intakes of biotin (35 mcg to 60 mcg/day) meet the dietary requirement (1).

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males (mcg/day)</th>
<th>Females (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
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<td>6</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>8</td>
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<tr>
<td>Children</td>
<td>4-8 years</td>
<td>12</td>
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<tr>
<td>Children</td>
<td>9-13 years</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14-18 years</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Adults</td>
<td>19 years and older</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>all ages</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>all ages</td>
<td>-</td>
<td>35</td>
</tr>
</tbody>
</table>

Disease Prevention

Birth defects

Research indicates that biotin is broken down more rapidly during pregnancy and that biotin nutritional status declines during the course of pregnancy (6). One study reported that biotin excretion dropped below the normal range during late pregnancy in six out of 13 women, suggesting that their biotin status was abnormally low. Over half of pregnant women have abnormally high excretion of a metabolite (3-hydroxyisovaleric acid) thought to reflect decreased activity of a biotin-dependent enzyme. A study of 26 pregnant women found that biotin supplementation decreased the excretion of this metabolite compared to placebo, suggesting that marginal biotin deficiency may be relatively common in pregnancy (14). In one study, the incidence of decreased lymphocyte propionyl-CoA carboxylase activity (a marker of biotin deficiency) in pregnancy was greater than 75% (18). Although the level of biotin depletion is not severe enough to cause diagnostic signs or symptoms, such observations are sources of concern because subclinical biotin deficiency has been shown to cause birth defects in several animal species (16). Currently, it is estimated that at least one third of women develop marginal biotin deficiency during pregnancy (8). Indirect evidence also suggests that marginal biotin deficiency causes birth defects in humans. On balance, the potential risk for teratogenesis (abnormal development of the embryo or fetus) from biotin deficiency makes it prudent to ensure adequate biotin intake throughout pregnancy. Since pregnant women are advised to consume supplemental folic acid prior to and during pregnancy (see Folic Acid) to prevent neural tube defects, it would be easy to consume supplemental biotin (at least 30 mcg/day) in the form of a multivitamin that also contains at least 400 mcg of folic acid. Toxicity at this level of biotin intake has never been reported (See Safety).
Disease Treatment

Diabetes mellitus

It has been known for many years that overt biotin deficiency impairs glucose utilization in rats (19). In one human study, blood biotin levels were significantly lower in 43 patients with non-insulin dependent diabetes mellitus (NIDDM; type 2 diabetes) than in non-diabetic control subjects, and lower fasting blood glucose levels were associated with higher blood biotin levels. After one month of biotin supplementation (9,000 mcg/day), fasting blood glucose levels decreased by an average of 45% (20). In contrast, a study in ten type 2 diabetics and seven nondiabetic controls reported that biotin supplementation (15,000 mcg/day) for 28 days did not decrease fasting blood glucose levels in either group (21). A more recent double-blind, placebo-controlled study by the same group of investigators found that the same biotin treatment protocol lowered plasma triglyceride levels in both diabetic and nondiabetic patients with hypertriglyceridemia (22). In this study, biotin administration did not affect blood glucose concentrations in either diabetic or nondiabetic subjects. Additionally, a few studies have shown that co-supplementation with biotin and chromium picolinate may be a beneficial adjunct therapy in patients with type 2 diabetes (23-26). However, several studies have reported that administration of chromium picolinate alone improves glycemic control in diabetic subjects (27). See the separate article on chromium.

Reductions in blood glucose levels were found in seven insulin-dependent (type 1) diabetics after one week of supplementation with 16,000 mcg of biotin daily (28). Several mechanisms could explain a possible blood glucose-lowering effect of biotin. As a cofactor of enzymes required for fatty acid synthesis, biotin may increase the utilization of glucose for fat synthesis. Biotin has been found to stimulate glucokinase, a liver enzyme that increases synthesis of glycogen, the storage form of glucose. Biotin has also been found to stimulate the secretion of insulin in the pancreas of rats, which also has the effect of lowering blood glucose (29). An effect on cellular glucose transporters (GLUT) is currently under investigation. Presently, studies of the effect of supplemental biotin on blood glucose levels in humans are extremely limited, but they highlight the need for further research.

Brittle fingernails

The finding that biotin supplements were effective in treating hoof abnormalities in horses and swine led to speculation that biotin supplements might also be helpful in strengthening brittle fingernails in humans. Three uncontrolled trials examining the effects of biotin supplementation (2.5 mg/day for up to six months) in women with brittle fingernails have been published (29-31). In two of the trials, subjective evidence of clinical improvement was reported in 67-91% of the participants available for follow-up at the end of the treatment period (29, 30). One trial that used scanning electron microscopy to assess fingernail thickness and splitting found that fingernail thickness increased by 25% and splitting decreased after biotin supplementation (31). Although the results of these small uncontrolled trials suggest that biotin supplements may be helpful in strengthening brittle nails, larger placebo-controlled trials are needed to assess the efficacy of high-dose biotin supplementation for the treatment of brittle fingernails.

Hair loss
Although hair loss is a symptom of severe biotin deficiency (see Deficiency), there are no published scientific studies that support the claim that high-dose biotin supplements are effective in preventing or treating hair loss in men or women.

Sources

Food sources

Biotin is found in many foods, but generally in lower amounts than other water-soluble vitamins. Egg yolk, liver, and yeast are rich sources of biotin. Large national nutritional surveys in the U.S. were unable to estimate biotin intake due to the scarcity of data regarding biotin content of food. Smaller studies estimate average daily intakes of biotin to be from 40 to 60 mcg/day in adults (1). The table below lists some rich sources of biotin along with their content in micrograms (mcg) (32). However, a recent publication that employed chemical rather than microbial assays reported quite different content for some common foods (33).

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Biotin (mcg) (32, 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yeast</td>
<td>1 packet (7 grams)</td>
<td>1.4-14</td>
</tr>
<tr>
<td>Bread, whole-wheat</td>
<td>1 slice</td>
<td>0.02-6</td>
</tr>
<tr>
<td>Egg, cooked</td>
<td>1 large</td>
<td>13-25</td>
</tr>
<tr>
<td>Cheese, cheddar</td>
<td>1 ounce</td>
<td>0.4-2</td>
</tr>
<tr>
<td>Liver, cooked</td>
<td>3 ounces*</td>
<td>27-35</td>
</tr>
<tr>
<td>Pork, cooked</td>
<td>3 ounces*</td>
<td>2-4</td>
</tr>
<tr>
<td>Salmon, cooked</td>
<td>3 ounces*</td>
<td>4-5</td>
</tr>
<tr>
<td>Avocado</td>
<td>1 whole</td>
<td>2-6</td>
</tr>
<tr>
<td>Raspberries</td>
<td>1 cup</td>
<td>0.2-2</td>
</tr>
<tr>
<td>Cauliflower, raw</td>
<td>1 cup</td>
<td>0.2-4</td>
</tr>
</tbody>
</table>

*A 3-ounce serving of meat is about the size of a deck of cards.

Bacterial synthesis

Most bacteria that normally colonize the small and large intestine (colon) synthesize biotin. Whether the biotin is released and absorbed by humans in meaningful amounts remains unknown. However, a specialized process for the uptake of biotin has been identified in cultured cells derived from the lining of the small bowel and colon (34), suggesting that humans may be able to absorb biotin produced by enteric bacteria—a phenomenon documented in swine.

Safety

Toxicity

Biotin is not known to be toxic. Oral biotin supplementation has been well-tolerated in doses up to 200,000 mcg/day in people with hereditary disorders of biotin metabolism (1). In people without disorders of biotin
metabolism, doses of up to 5,000 mcg/day for two years were not associated with adverse effects (35). However, there is one case report of life-threatening eosinophilic pleuropericardial effusion in an elderly woman who took a combination of 10,000 mcg/day of biotin and 300 mg/day of pantothenic acid for two months (36). Due to the lack of reports of adverse effects when the Dietary Reference Intakes (DRI) were established for biotin in 1998, the Institute of Medicine did not establish a tolerable upper level of intake (UL) for biotin (1).

Note: 1 mg = 1,000 mcg.

**Nutrient interactions**

Large doses of pantothenic acid (vitamin B₅) have the potential to compete with biotin for intestinal and cellular uptake due to their similar structures (37). In addition, very high (pharmacologic) doses of lipoic acid have been found to decrease the activity of biotin-dependent carboxylases in rats, but such an effect has not been demonstrated in humans (4, 38).

**Drug interactions**

Individuals on long-term anticonvulsant (anti-seizure) therapy reportedly have reduced blood levels of biotin as well as increased urinary excretion of organic acids that indicated decreased carboxylase activity (39). The anticonvulsants primidone and carbamazepine inhibit biotin absorption in the small intestine. Chronic therapy with phenobarbital, phenytoin, or carbamazepine appears to increase urinary excretion of 3-hydroxyisovaleric acid. Use of the anticonvulsant valproic acid has been associated with decreased biotinidase activity in children (17). Long-term treatment with sulfa drugs or other antibiotics may decrease bacterial synthesis of biotin, theoretically increasing the requirement for dietary biotin.

**Linus Pauling Institute Recommendation**

Little is known regarding the amount of dietary biotin required to promote optimal health or prevent chronic disease. The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 30 micrograms (mcg) of biotin/day for adults. A varied diet should provide enough biotin for most people. However, following the Linus Pauling Institute recommendation to take a daily multivitamin-mineral supplement will generally provide an intake of at least 30 mcg of biotin/day.

**Older adults (65 years and older)**

Presently, there is no indication that older adults have an increased requirement for biotin. If dietary biotin intake is not sufficient, a daily multivitamin-mineral supplement will generally provide an intake of at least 30 mcg of biotin/day.

**References**

Written in June 2004 by:
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Linus Pauling Institute
Oregon State University
**Folic Acid**

The terms folic acid and folate are often used interchangeably for this water-soluble B-complex vitamin. Folic acid, the more stable form, occurs rarely in foods or the human body but is the form most often used in vitamin supplements and fortified foods. Naturally occurring folates exist in many chemical forms. Folates are found in foods as well as in metabolically active forms in the human body (1). In the following discussion forms found in food or the body will be referred to as "folates", while the form found in supplements or fortified foods will be referred to as "folic acid."

**Function**

**One-carbon metabolism**

The only function of folate coenzymes in the body appears to be in mediating the transfer of one-carbon units (2). Folate coenzymes act as acceptors and donors of one-carbon units in a variety of reactions critical to the metabolism of nucleic acids and amino acids (3).

**Nucleic acid metabolism**

Folate coenzymes play a vital role in DNA metabolism through two different pathways. 1) The synthesis of DNA from its precursors (thymidine and purines) is dependent on folate coenzymes. 2) A folate coenzyme is required for the synthesis of methionine, and methionine is required for the synthesis of S-adenosylmethionine (SAM). SAM is a methyl group (one-carbon unit) donor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA. Methylation of DNA may be important in cancer prevention (see Disease Prevention).

**Amino acid metabolism**

Folate coenzymes are required for the metabolism of several important amino acids. The synthesis of methionine from homocysteine requires a folate coenzyme as well as a vitamin B₁₂-dependent enzyme. Thus, folate deficiency can result in decreased synthesis of methionine and a buildup of homocysteine. Increased levels of homocysteine may be a risk factor for heart disease as well as several other chronic diseases (see Disease Prevention).

**Nutrient interactions**

**Vitamin B₁₂ and vitamin B₆**

The metabolism of homocysteine, an intermediate in the metabolism of sulfur-containing amino acids, provides an example of the interrelationships among nutrients necessary for optimum physiological function and health. Healthy individuals utilize two different pathways to metabolize homocysteine (see diagram). One pathway (methionine synthase) synthesizes methionine from homocysteine and is dependent on a folate coenzyme and a vitamin B₁₂-dependent enzyme. The other pathway converts homocysteine to another amino acid, cysteine, and requires two vitamin B₆-dependent enzymes. Thus, the amount of homocysteine in the blood is regulated by three vitamins: folate, vitamin B₁₂, and vitamin B₆ (4).
Deficiency

Causes

Folate deficiency is most often caused by a dietary insufficiency; however, folate deficiency can occur in a number of other situations. For example, alcoholism is associated with low dietary intake and diminished absorption of folate, which can lead to folate deficiency. Additionally, certain conditions such as pregnancy or cancer result in increased rates of cell division and metabolism, causing an increase in the body's demand for folate (5). Several medications may also contribute to deficiency (see Drug interactions).

Symptoms

Individuals in the early stages of folate deficiency may not show obvious symptoms, but blood levels of homocysteine may increase (see Prevention). Rapidly dividing cells are most vulnerable to the effects of folate deficiency; thus, when the folate supply to the rapidly dividing cells of the bone marrow is inadequate, blood cell division becomes abnormal resulting in fewer but larger red blood cells. This type of anemia is called megaloblastic or macrocytic anemia, referring to the enlarged, immature red blood cells. Neutrophils, a type of white blood cell, become hypersegmented, a change which can be found by examining a blood sample microscopically. Because normal red blood cells have a lifetime in the circulation of approximately four months, it can take months for folate deficient individuals to develop the characteristic megaloblastic anemia. Progression of such anemia leads to a decreased oxygen carrying capacity of the blood and may ultimately result in symptoms of fatigue, weakness, and shortness of breath (1). It is important to point out that megaloblastic anemia resulting from folate deficiency is identical to the megaloblastic anemia resulting from vitamin B12 deficiency, and further clinical testing is required to diagnose the true cause of megaloblastic anemia.

The Recommended Dietary Allowance (RDA)

Determination of the RDA

Traditionally, the dietary folate requirement was defined as the amount needed to prevent a deficiency severe enough to cause symptoms like anemia. The most recent RDA (1998) was based primarily on the adequacy of red blood cell folate concentrations at different levels of folate intake, as judged by the absence of abnormal hematological indicators. Red cell folate has been shown to correlate with liver folate stores. Maintenance of normal blood homocysteine levels, an indicator of one-carbon metabolism, was considered only as an ancillary indicator of adequate folate intake. Because pregnancy is associated with a significant increase in cell division and other metabolic processes that require folate coenzymes, the RDA for pregnant women is considerably higher than for women who are not pregnant (3). However, the prevention of neural tube defects (NTD) was not considered when setting the RDA for pregnant women. Rather, reducing the risk of NTD was considered in a separate recommendation for women capable of becoming pregnant (see Prevention), because the crucial events in the development of the neural tube occur before many women are aware that they are pregnant (6).

Dietary Folate Equivalents (DFE)
When the Food and Nutrition Board of the Institute of Medicine set the new dietary recommendation for folate, they introduced a new unit, the Dietary Folate Equivalent (DFE). Use of the DFE reflects the higher bioavailability of synthetic folic acid found in supplements and fortified foods compared to that of naturally occurring food folates (6).

- 1 microgram (mcg) of food folate provides 1 mcg of DFE
- 1 mcg of folic acid taken with meals or as fortified food provides 1.7 mcg of DFE
- 1 mcg of folic acid (supplement) taken on an empty stomach provides 2 mcg of DFE

For example, a serving of food containing 60 mcg of folate would provide 60 mcg of DFE, while a serving of pasta fortified with 60 mcg of folic acid would provide $1.7 \times 60 = 102$ mcg DFE due to the higher bioavailability of folic acid. A folic acid supplement of 400 mcg taken on an empty stomach would provide 800 mcg of DFE. It should be noted that DFEs were determined in studies with adults and whether folic acid in infant formula is more bioavailable than folates in mother's milk has not been studied. Use of DFEs to determine a folic acid requirement for the infant would not be desirable.

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males (mcg/day)</th>
<th>Females (mcg/day)</th>
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<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>65 (AI)</td>
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<td>9-13 years</td>
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<td>Pregnancy</td>
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</tr>
<tr>
<td>Breast-feeding</td>
<td>all ages</td>
<td>-</td>
<td>500</td>
</tr>
</tbody>
</table>

**Genetic variation in folate requirements**

A common polymorphism or variation in the gene for the enzyme methylene tetrahydrofolate reductase (MTHFR), known as the C677T MTHFR polymorphism, results in a less stable enzyme (7). Depending on the population, 50% of individuals may have inherited one copy (C/T), and 5% to 25% of individuals may have inherited two copies (T/T) of the abnormal MTHFR gene. MTHFR plays an important role in maintaining the specific folate coenzyme required to form methionine from homocysteine (see diagram). When folate intake is low, individuals who are homozygous (T/T) for the abnormal gene have lower levels of the MTHFR enzyme and thus higher levels of homocysteine in their blood (8). Improved folate nutritional status appears to stabilize the MTHFR enzyme, resulting in improved enzyme levels and lower homocysteine levels. An important unanswered question about folate is whether the present RDA is enough to normalize MTHFR enzyme levels in individuals who are homozygous for the C677T polymorphism, or whether those individuals have a higher folate requirement than the RDA (9).
Disease Prevention

Pregnancy complications

**Neural tube defects**

Fetal growth and development are characterized by widespread cell division. Adequate folate is critical for DNA and RNA synthesis. Neural tube defects (NTD) result in either anencephaly or spina bifida, which are devastating and sometimes fatal birth defects. The defects occur between the 21\textsuperscript{st} and 27\textsuperscript{th} days after conception, a time when many women do not realize they are pregnant (10). The risk of NTD in the United States prior to fortification of foods with folic acid was estimated to be one per 1000 pregnancies (1). Results of randomized trials have demonstrated 60% to 100% reductions in NTD cases when women consumed folic acid supplements in addition to a varied diet during the periconceptional period (about one month before and one month after conception). The results of these and other studies prompted the U.S. Public Health Service to recommend that all women capable of becoming pregnant consume 400 mcg of folic acid daily to prevent NTD. The recommendation was made to all women of childbearing age because adequate folic acid must be available very early in pregnancy, and because many pregnancies in the U.S. are unplanned. Despite the effectiveness of folic acid supplementation, it appears that less than half of women who become pregnant follow the recommendation (11). To decrease the incidence of NTD, the FDA implemented legislation in 1998 requiring the fortification of all enriched grain products with folic acid (see Sources). The required level of folic acid fortification in the U.S. was estimated to provide 100 mcg of additional folic acid in the average person's diet, though it probably provides even more due to overuse of folic acid by food manufacturers (9). The Centers for Disease Control and Prevention reported that the frequency of NTD in the U.S. has decreased 26% since the mandate (12). However, studies in Canada, where fortification is nearly identical to that in the U.S. (1.5 and 1.4 mg of folic acid/kg of grain, respectively), have reported greater reductions in the incidence of NTD. In fact, it was recently proposed that the fortification legislation has prevented approximately 50% of NTD in Canada and the U.S, but improvements in the U.S. have been largely underestimated (13).

Other pregnancy complications

Adequate folate status may also prevent the occurrence of other types of birth defects, including certain heart defects and limb malformations. However, the support for these findings is not as consistent or clear as support for NTD prevention (10). Additionally, low levels of dietary folate during pregnancy have been associated with increased risks of premature delivery and infant low infant birth weights. More recently, elevated blood homocysteine levels, considered an indicator of functional folate deficiency, have been associated with increased incidence of miscarriage as well as pregnancy complications like preeclampsia and placental abruption (14). Thus, it is reasonable to maintain folic acid supplementation throughout pregnancy, even after closure of the neural tube in order to decrease the risk of other problems during pregnancy.

Cardiovascular disease

**Homocysteine and cardiovascular disease**

The results of more than 80 studies indicate that even moderately elevated levels of homocysteine in the blood increase the risk of cardiovascular diseases (4). An analysis of the observational studies on blood homocysteine...
and vascular disease indicated that a prolonged decrease in plasma homocysteine level of only 1 micromole/liter resulted in about a 10% risk reduction (15). The mechanism by which homocysteine increases the risk of vascular disease remains the subject of a great deal of research, but it may involve adverse effects of homocysteine on blood clotting, arterial vasodilation, and thickening of arterial walls (16). Although increased homocysteine levels in the blood have been consistently associated with increased risk of cardiovascular diseases, it is not yet clear whether lowering homocysteine levels will reduce cardiovascular disease risk (see below, Folate and homocysteine). Consequently, the American Heart Association recommends screening for elevated total homocysteine levels only in "high risk" individuals, for example those with personal or family history of premature cardiovascular disease, malnutrition or malabsorption syndromes, hypothyroidism, kidney failure, lupus, or individuals taking certain medications (nicotinic acid, theophylline, bile acid-binding resins, methotrexate, and L-dopa). Most research indicates that a plasma homocysteine level of < 10 micromoles/liter is associated with a lower risk of cardiovascular disease and a reasonable treatment goal for individuals at high risk (17).

**Folate and homocysteine**

Folate-rich diets have been associated with decreased risk of cardiovascular disease. A study that followed 1,980 Finnish men for ten years found that those who consumed the most dietary folate had a 55% lower risk of an acute coronary event when compared with those who consumed the least dietary folate (18). Of the three vitamins that regulate homocysteine levels, folic acid has been shown to have the greatest effect in lowering basal levels of homocysteine in the blood when there is no coexisting deficiency of vitamin B12 or vitamin B6 (see Nutrient interactions). Increasing folate intake through folate-rich foods or supplements has been found to lower homocysteine levels. Moreover, blood homocysteine levels have declined since the FDA mandated folic acid fortification of the grain supply (9). A recent meta-analysis of 25 randomized controlled trials found that supplementation with 0.8 mg folic acid daily maximally reduced plasma homocysteine concentrations; daily doses of 0.2 mg and 0.4 mg of folic acid were associated with 60% and 90% reductions, respectively, in plasma homocysteine (19). A supplement regimen of 400 mcg of folic acid, 2 mg of vitamin B6, and 6 mcg of vitamin B12 has been advocated by the American Heart Association if an initial trial of a folate-rich diet (see Sources) is not successful in adequately lowering homocysteine levels (17). Although increased folic acid intake has been found to decrease homocysteine levels, it is presently not clear whether increasing folic acid intake results in decreased risk of cardiovascular diseases. Several randomized placebo-controlled trials have been conducted or are ongoing to determine whether homocysteine lowering through folic acid and other B vitamin supplementation reduces the incidence of cardiovascular diseases. A preliminary meta-analysis of data from four of the ongoing trials, including about 14,000 subjects, showed that B vitamin supplementation had no significant effect on risk of coronary heart disease or stroke (20). Similarly, another meta-analysis of 12 randomized controlled trials, including data from 16,958 individuals with preexisting cardiovascular or renal disease, found that folic acid supplementation had no effect on coronary heart disease, stroke, or all-cause mortality despite 13%-52% reductions in plasma homocysteine concentrations (21). Consequently, the American Heart Association removed its recommendation for using folic acid to prevent cardiovascular diseases in high-risk women (22). Completion of the ongoing clinical trials should provide a more definitive answer whether folic acid is beneficial for the prevention or treatment of heart disease or stroke.

**Cancer**

Cancer is thought to arise from DNA damage in excess of ongoing DNA repair and/or the inappropriate expression of critical genes. Because of the important roles played by folate in DNA and RNA synthesis and
methylation, it is possible for folate intake to affect both DNA repair and gene expression. The consumption of at least five servings of fruits and vegetables daily has been consistently associated with a decreased incidence of cancer. Fruits and vegetables are excellent sources of folate, which may play a role in their anti-carcinogenic effect. Observational studies have found diminished folate status to be associated with cancers of the cervix, colon and rectum, lung, esophagus, brain, pancreas, and breast. Intervention trials of folic acid supplementation in humans have been conducted mainly with respect to cervical and colorectal (colon and rectal) cancer. While the results in cervical cancer have been inconsistent (2), randomized intervention trials regarding colorectal cancer have been more promising (23, 24).

Colorectal cancer

A recent meta-analysis of seven cohort and nine case-control studies found that folate from foods was inversely associated with colorectal cancer risk; however, total folate from foods and folic acid supplements was not associated with colorectal cancer risk (25). It is important to note that the case-control studies examined in this meta-analysis were highly heterogeneous, and that the authors stated that dietary fiber or other vitamins could have confounded their results. Overall, the role of folate in the possible prevention of colorectal cancer provides an example of the complexity of the interactions between genetics and nutrition. In general, observational studies have found that relatively low folate intake and high alcohol intake are associated with increased incidence of colorectal cancer (1, 26, 27). Alcohol interferes with the absorption and metabolism of folate (5).

In a prospective study of more than 45,000 male health professionals, current intake of more than two alcoholic drinks per day doubled the risk of colon cancer. The combination of high alcohol and low folate intake yielded an even greater risk of colon cancer; however, increased alcohol intake in individuals who consumed 650 mcg or more of folate per day was not associated with an increased risk of colon cancer (28). In some studies, individuals who are homozygous for the C677T MTHFR polymorphism (TT) have been found to be at decreased risk for colon cancer when folate intake is adequate. However, when folate intake is low and/or alcohol intake is high, individuals with the (T/T) genotype have been found to be at increased risk of colorectal cancer (29, 30).

While dietary folate may be protective against colorectal cancer, high doses of supplemental folic acid may actually accelerate tumor growth in cancer patients. A recent chemopreventive trial in patients with a history of colorectal adenoma associated supplementation of 1 mg/day of folic acid (more than twice the RDA) with a statistical trend for advanced colorectal lesions as well as with a significantly increased risk (>2-fold) for the presence of three or more colorectal adenomas (31). In this study, folic acid supplementation was also associated with an increased risk for cancers at other sites, primarily the prostate. Human observational studies as well as animal studies on high-dose folate and cancer have reported mixed results. Thus, more research is needed to determine the role of high-dose folate in cancer progression.

Breast cancer

Studies investigating whether folate intake affects breast cancer risk have reported mixed results (32). The results of two prospective studies suggest that increased folate intake may reduce the risk of breast cancer in women who regularly consume alcohol (33-35); moderate alcohol intake has been associated with increased risk of breast cancer in women in several studies. Interestingly, a very large prospective study in more than 88,000 nurses reported that folic acid intake was not associated with breast cancer in women who consumed less than one alcoholic drink per day. However, in women consuming at least one alcoholic drink per day, folic acid intake of at least 600 mcg daily resulted in about half the risk of breast cancer compared with women who consumed less that 300 mcg of folic acid daily (35).
Alzheimer's disease and cognitive impairment

The role of folate in nucleic acid synthesis and methylation reactions is essential for normal brain function. Over the past decade several investigators have described associations between decreased folate levels and cognitive impairment in the elderly (36). A large cross-sectional study in elderly Canadians found that those individuals with low serum folate levels were more likely to have dementia, be institutionalized, and be depressed. However, these findings could reflect the poorer nutritional status of institutionalized elderly and individuals with dementia. In the same study, low serum folate levels were associated with an increased likelihood of short-term memory problems in elderly individuals who had no signs of dementia (37). A study in 30 elderly nuns, who lived in the same convent, ate the same diet, and had similar lifestyles, reported a strong association between decreased blood folate levels and the severity of brain atrophy related to Alzheimer's disease (38). More recent studies have reported conflicting results as to whether folate status impacts Alzheimer's disease risk. One study in elderly people of predominantly Hispanic and African-American ethnicity with a high prevalence of vascular risk factors reported that a higher folate intake, from diet and folic acid supplements, was associated with a decreased risk for Alzheimer's disease (39). In contrast, a prospective study in elderly individuals reported that dietary folate is not associated with Alzheimer's disease (40), whereas another prospective study reported that a high folate intake, from foods and from folic acid supplements, was associated with increased rates of cognitive decline in the elderly (41). Moderately increased homocysteine levels, as well as decreased folate and vitamin B12 levels, have been associated with Alzheimer’s disease and vascular dementia. One study in 370 elderly men and women, who were followed over three years, associated low serum levels of vitamin B12 (< 150 pmol/L) or folate (< 10 nmol/L) with a doubling of the risk of developing Alzheimer’s disease (42). In a sample of 1,092 men and women without dementia followed for an average of ten years, those with higher plasma homocysteine levels at baseline had a significantly higher risk of developing Alzheimer’s disease and other types of dementia (43). Those with plasma homocysteine levels greater than 14 micromoles/liter had nearly twice the risk of developing Alzheimer’s disease.

Sources

Food sources

Green leafy vegetables (foliage) are rich sources of folate and provide the basis for its name. Citrus fruit juices, legumes, and fortified cereals are also excellent sources of folate (1). A number of folate-rich foods are listed in the table below along with their folate content in micrograms (mcg). For more information on the nutrient content of specific foods, search the USDA food composition database.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Folate (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified breakfast cereal</td>
<td>1 cup</td>
<td>200-400</td>
</tr>
<tr>
<td>Orange juice (from concentrate)</td>
<td>6 ounces</td>
<td>83</td>
</tr>
<tr>
<td>Spinach (cooked)</td>
<td>1/2 cup</td>
<td>132</td>
</tr>
<tr>
<td>Asparagus (cooked)</td>
<td>1/2 cup (~ 6 spears)</td>
<td>134</td>
</tr>
<tr>
<td>Lentils (cooked)</td>
<td>1/2 cup</td>
<td>179</td>
</tr>
<tr>
<td>Garbanzo beans (cooked)</td>
<td>1/2 cup</td>
<td>141</td>
</tr>
<tr>
<td>Lima beans (cooked)</td>
<td>1/2 cup</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>-------</td>
<td>----------</td>
</tr>
<tr>
<td>Bread</td>
<td>1 slice</td>
<td>20 (Folic acid)*</td>
</tr>
<tr>
<td>Pasta (cooked)</td>
<td>1 cup</td>
<td>60 (Folic acid)*</td>
</tr>
<tr>
<td>Rice (cooked)</td>
<td>1 cup</td>
<td>60 (Folic acid)*</td>
</tr>
</tbody>
</table>

*To help prevent neural tube defects, the FDA required the addition of 1.4 milligrams (mg) of folic acid per kilogram (kg) of grain to be added to refined grain products, which are already enriched with niacin, thiamin, riboflavin, and iron, as of January 1, 1998. The addition of nutrients to foods in order to prevent a nutritional deficiency or restore nutrients lost in processing is known as fortification. It has been estimated that this level of fortification increases dietary intake by an average of 100 mcg folic acid/day (10). For more information on folic acid fortification, review the FDA fact sheet.

**Supplements**

The principal form of supplementary folate is folic acid. It is available in single ingredient and combination products such as B-complex vitamins and multivitamins. Doses equal to or greater than 1 mg require a prescription (44).

**Safety**

**Toxicity**

No adverse effects have been associated with the consumption of excess folate from foods. Concerns regarding safety are limited to synthetic folic acid intake. Deficiency of vitamin B₁₂, though often undiagnosed, may affect a significant number of people, especially older adults (see Vitamin B₁₂). One symptom of vitamin B₁₂ deficiency is megaloblastic anemia, which is indistinguishable from that associated with folate deficiency (see Deficiency). Large doses of folic acid given to an individual with an undiagnosed vitamin B₁₂ deficiency could correct megaloblastic anemia without correcting the underlying vitamin B₁₂ deficiency, leaving the individual at risk of developing irreversible neurologic damage. Such cases of neurologic progression in vitamin B₁₂ deficiency have been mostly seen at folic acid doses of 5,000 mcg (5 mg) and above. In order to be very sure of preventing irreversible neurological damage in vitamin B₁₂ deficient individuals, the Food and Nutrition Board of the Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1,000 mcg (1 mg daily). The board also noted that vitamin B₁₂ deficiency is very rare in women in their childbearing years, making the consumption of folic acid at or above 1000 mcg/day unlikely to cause problems (1); however, there are limited data on the effects of large doses.

**Tolerable Upper Intake Level (UL) for Folic Acid**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>UL (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-12 months</td>
<td>Not possible to establish*</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>300</td>
</tr>
<tr>
<td>Children 4-8 years</td>
<td>400</td>
</tr>
<tr>
<td>Children 9-13 years</td>
<td>600</td>
</tr>
<tr>
<td>Adolescents 14-18 years</td>
<td>800</td>
</tr>
</tbody>
</table>
Drug interactions

When nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin or ibuprofen, are taken in very large therapeutic dosages (i.e., to treat severe arthritis), they may interfere with folate metabolism. In contrast, routine low dose use of NSAIDs has not been found to adversely affect folate status. The anticonvulsant, phenytoin, has been shown to inhibit the intestinal absorption of folate, and several studies have associated decreased folate status with long-term use of the anticonvulsants, phenytoin, phenobarbital, and primidone (45). However, few studies controlled for differences in dietary folate intake between anticonvulsant users and nonusers. Also, taking folic acid at the same time as the cholesterol-lowering agents, cholestyramine and colestipol, may decrease the absorption of folic acid (44). Methotrexate is a folic acid antagonist used to treat a number of diseases, including rheumatoid arthritis and psoriasis. Some of the side effects of methotrexate are similar to those of severe folate deficiency, and increased dietary folate or supplemental folic acid may decrease side effects without reducing the efficacy of methotrexate. A number of other medications have been shown to have antifolate activity, including trimethoprim (an antibiotic), pyrimethamine (an antimalarial), triamterene (a blood pressure medication), and sulfasalazine (a treatment for ulcerative colitis). Early studies of oral contraceptives (birth control pills) containing high doses of estrogen indicated adverse effects on folate status; however, this finding has not been supported by more recent studies on low dose oral contraceptives that controlled for dietary folate (1).

Linus Pauling Institute Recommendation

The available scientific evidence shows that adequate folate intake prevents neural tube defects and other poor outcomes of pregnancy, is helpful in lowering the risk of some forms of cancer, especially in genetically susceptible individuals, and may lower the risk of cardiovascular diseases. The Linus Pauling Institute recommends that adults take a 400 mcg supplement of folic acid daily, in addition to folate and folic acid consumed in the diet. A daily multivitamin-mineral supplement, containing 100% of the Daily Value (DV) for folic acid provides 400 mcg of folic acid. Even with a larger than average intake of folic acid from fortified foods, it is unlikely that an individual’s daily folate intake would regularly exceed the tolerable upper intake level of 1,000 mcg/day established by the Food and Nutrition Board (see Safety).

Older adults (65 years and older)

The recommendation for 400 mcg/day of supplemental folic acid as part of a daily multivitamin-multimineral supplement, in addition to a folate-rich diet, is especially important for older adults because blood homocysteine levels tend to increase with age (see Disease Prevention).

References

Written in April 2002 by:
Jane Higdon, Ph.D.
Riboflavin

Riboflavin is a water-soluble B vitamin, also known as vitamin B\textsubscript{2}. In the body, riboflavin is primarily found as an integral component of the coenzymes, flavin adenine dinucleotide (FAD) and flavin mononucleotide (FMN) (1). Coenzymes derived from riboflavin are termed flavocoenzymes, and enzymes that use a flavocoenzyme are called flavoproteins (2).

Function

Oxidation-reduction (redox) reactions

Living organisms derive most of their energy from oxidation-reduction (redox) reactions, which are processes that involve the transfer of electrons. Flavocoenzymes participate in redox reactions in numerous metabolic pathways (3). Flavocoenzymes are critical for the metabolism of carbohydrates, fats, and proteins. FAD is part of the electron transport (respiratory) chain, which is central to energy production. In conjunction with cytochrome P-450, flavocoenzymes also participate in the metabolism of drugs and toxins (4).

Antioxidant functions

Glutathione reductase is a FAD-dependent enzyme that participates in the redox cycle of glutathione. The glutathione redox cycle plays a major role in protecting organisms from reactive oxygen species, such as hydroperoxides. Glutathione reductase requires FAD to regenerate two molecules of reduced glutathione from oxidized glutathione. Riboflavin deficiency has been associated with increased oxidative stress (4). Measurement of glutathione reductase activity in red blood cells is commonly used to assess riboflavin nutritional status (5).

Glutathione peroxidase, a selenium-containing enzyme, requires two molecules of reduced glutathione to break down hydroperoxides (see diagram).

Xanthine oxidase, another FAD-dependent enzyme, catalyzes the oxidation of hypoxanthine and xanthine to uric acid. Uric acid is one of the most effective water-soluble antioxidants in the blood. Riboflavin deficiency can result in decreased xanthine oxidase activity, reducing blood uric acid levels (6).

Nutrient Interactions

B-complex vitamins

Because flavoproteins are involved in the metabolism of several other vitamins (vitamin B\textsubscript{6}, niacin, and folic acid), severe riboflavin deficiency may affect many enzyme systems. Conversion of most naturally available vitamin B\textsubscript{6} to its coenzyme form, pyridoxal 5′-phosphate (PLP), requires the FMN-dependent enzyme, pyridoxine 5′-phosphate oxidase (PPO) (7). At least two studies in the elderly have documented significant interactions between indicators of vitamin B\textsubscript{6} and riboflavin nutritional status (8, 9). The synthesis of the niacin-containing coenzymes, NAD and NADP, from the amino acid, tryptophan, requires the FAD-dependent enzyme, kynurenine mono-oxygenase. Severe riboflavin deficiency can decrease the conversion of tryptophan to NAD and NADP, increasing the risk of niacin deficiency (3). Methylene tetrahydrofolate reductase (MTHFR) is a FAD-
dependent enzyme that plays an important role in maintaining the specific folate coenzyme required to form \textit{methionine} from \textit{homocysteine} (see \textit{diagram}). Along with other B vitamins, increased riboflavin intake has been associated with decreased plasma homocysteine levels (10). Recently, increased plasma riboflavin levels were associated with decreased plasma homocysteine levels, mainly in individuals \textit{homozygous} for the C677T \textbf{polymorphism} of the MTHFR gene and in individuals with low folate intake (11). Such results illustrate that chronic disease risk may be influenced by complex interactions between genetic and dietary factors.

**Iron**

Riboflavin deficiency alters \textit{iron} metabolism. Although the mechanism is not clear, research in animals suggests that riboflavin deficiency may impair iron absorption, increase intestinal loss of iron, and/or impair iron utilization for the synthesis of \textit{hemoglobin}. In humans, improving riboflavin nutritional status has been found to increase circulating hemoglobin levels. Correction of riboflavin deficiency in individuals who are both riboflavin and iron deficient improves the response of iron-deficiency anemia to iron therapy (12).

**Deficiency**

Ariboflavinosis is the medical name for clinical riboflavin deficiency. Riboflavin deficiency is rarely found in isolation; it occurs frequently in combination with deficiencies of other water-soluble vitamins. Symptoms of riboflavin deficiency include sore throat, redness and swelling of the lining of the mouth and throat, cracks or sores on the outsides of the lips (cheliosis) and at the corners of the mouth (angular stomatitis), inflammation and redness of the tongue (magenta tongue), and a moist, scaly skin inflammation (seborrheic dermatitis). Other symptoms may involve the formation of blood vessels in the clear covering of the eye (vascularization of the cornea) and decreased red blood cell count in which the existing red blood cells contain normal levels of hemoglobin and are of normal size (normochromic normocytic anemia) (1, 3). Severe riboflavin deficiency may result in decreased conversion of vitamin B\textsubscript{6} to its \textit{coenzyme} form (PLP) and decreased conversion of tryptophan to niacin (see \textit{Nutrient Interactions}).

**Preeclampsia** is defined as the presence of elevated blood pressure, protein in the urine, and \textit{edema} (significant swelling) during pregnancy. About 5% of women with preeclampsia may progress to eclampsia, a significant cause of maternal death. Eclampsia is characterized by seizures, in addition to high blood pressure and increased risk of hemorrhage (severe bleeding) (13). A study in 154 pregnant women at increased risk of preeclampsia found that those who were riboflavin deficient were 4.7 times more likely to develop preeclampsia than those who had adequate riboflavin nutritional status. The cause of preeclampsia-eclampsia is not known. Decreased intracellular levels of flavocoenzymes could cause \textit{mitochondrial} dysfunction, increase \textit{oxidative stress}, and interfere with nitric oxide release and thus blood vessel dilation—all of these changes have been associated with preeclampsia (14). However, a small \textit{randomized}, \textit{placebo}-controlled, \textit{double-blind} trial in 450 pregnant women with prior preeclampsia found that supplementation with 15 mg of riboflavin daily did not prevent the condition (15).

**Risk factors for riboflavin deficiency**

Alcoholics are at increased risk for riboflavin deficiency due to decreased intake, decreased absorption, and impaired utilization of riboflavin. Additionally, anorexic individuals rarely consume adequate riboflavin, and lactose intolerant individuals may not consume milk or other dairy products which are good sources of
The conversion of riboflavin into FAD and FMN is impaired in hypothyroidism and adrenal insufficiency (3, 4). Further, people who are very active physically (athletes, laborers) may have a slightly increased riboflavin requirement. However, riboflavin supplementation has not generally been found to increase exercise tolerance or performance (16).

The Recommended Dietary Allowance (RDA)

The RDA for riboflavin, revised in 1998, was based on the prevention of deficiency. Clinical signs of deficiency in humans appear at intakes of less than 0.5-0.6 milligrams (mg)/day, and urinary excretion of riboflavin is seen at intake levels of approximately 1 mg/day (1).

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>0.3 (AI)</td>
<td>0.3 (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
<td>0.4 (AI)</td>
<td>0.4 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Children</td>
<td>4-8 years</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Children</td>
<td>9-13 years</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14-18 years</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Adults</td>
<td>19 years and older</td>
<td>1.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>all ages</td>
<td>-</td>
<td>1.4</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>all ages</td>
<td>-</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Disease Prevention

Cataracts

Age-related cataracts are the leading cause of visual disability in the U.S. and other developed countries. Research has focused on the role of nutritional antioxidants because of evidence that light-induced oxidative damage of lens proteins may lead to the development of age-related cataracts. A case-control study found significantly decreased risk of age-related cataract (33% to 51%) in men and women in the highest quintile of dietary riboflavin intake (median of 1.6 to 2.2 mg/day) compared to those in the lowest quintile (median of 0.08 mg/day in both men and women) (17). Another case-control study reported that individuals in the highest quintile of riboflavin nutritional status, as measured by red blood cell glutathione reductase activity, had approximately one half the occurrence of age-related cataract as those in the lowest quintile of riboflavin status, though the results were not statistically significant (18). A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of riboflavin intake were 50% less likely to have cataracts than those in the lowest quintile (19). A prospective study of more than 50,000 women did not observe a difference between rates of cataract extraction between women in the highest quintile of riboflavin intake (median of 1.5 mg/day) and women in the lowest quintile (median of 1.2 mg/day) (20).
However, the range between the highest and lowest quintiles was small, and median intake levels for both quintiles were above the current RDA for riboflavin. A recent study in 408 women found that higher dietary intakes of riboflavin were inversely associated with five-year change in lens opacification (21). Although these observational studies provide support for the role of riboflavin in the prevention of cataracts, placebo-controlled intervention trials are needed to confirm the relationship.

**Disease Treatment**

**Migraine headaches**

Some evidence indicates that impaired mitochondrial oxygen metabolism in the brain may play a role in the pathology of migraine headaches. Because riboflavin is the precursor of the two flavoenzymes (FAD and FMN) required by the flavoproteins of the mitochondrial electron transport chain, supplemental riboflavin has been investigated as a treatment for migraine. A randomized placebo-controlled trial examined the effect of 400 mg of riboflavin/day for three months on migraine prevention in 54 men and women with a history of recurrent migraine headaches (22). Riboflavin was significantly better than placebo in reducing attack frequency and the number of headache days, though the beneficial effect was most pronounced during the third month of treatment. A more recent study by the same investigators found that treatment with either a medication called a beta-blocker or high-dose riboflavin resulted in clinical improvement, but each therapy appeared to act on a distinct pathological mechanism: beta-blockers on abnormal cortical information processing and riboflavin on decreased brain mitochondrial energy reserve (23). A small study in 23 patients reported a reduction in median migraine attack frequency after supplementation with 400 mg of riboflavin daily for three months (24). However, a randomized, double-blind, placebo-controlled study that administered a combination of riboflavin (400 mg/day), magnesium, and feverfew to migraine sufferers reported no therapeutic benefit compared to those administered a placebo containing 25 mg/day of riboflavin (25). It should be noted that only about 25 mg of riboflavin can be absorbed in a single oral dose (26). Although these findings are preliminary, data from most studies to date suggest that riboflavin supplementation might be a useful adjunct to pharmacologic therapy in migraine prevention.

**Sources**

**Food sources**

Most plant and animal derived foods contain at least small quantities of riboflavin. In the U.S., wheat flour and bread have been enriched with riboflavin (as well as thiamin, niacin, and iron) since 1943. Data from large dietary surveys indicate that the average intake of riboflavin for men is about 2 mg/day and for women is about 1.5 mg/day; both intakes are well above the RDA. Intake levels were similar for a population of elderly men and women (1). Riboflavin is easily destroyed by exposure to light. For instance, up to 50% of the riboflavin in milk contained in a clear glass bottle can be destroyed after two hours of exposure to bright sunlight (6). Some foods with substantial amounts of riboflavin are listed in the table below along with their riboflavin content in milligrams (mg). For more information on the nutrient content of foods, search the USDA food composition database.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Riboflavin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified cereal</td>
<td>1 cup</td>
<td>0.59 to 2.27</td>
</tr>
<tr>
<td>Food Item</td>
<td>Serving Size</td>
<td>Riboflavin (mg)</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Milk (nonfat)</td>
<td>1 cup (8 ounces)</td>
<td>0.34</td>
</tr>
<tr>
<td>Cheddar cheese</td>
<td>1 ounce</td>
<td>0.11</td>
</tr>
<tr>
<td>Egg (cooked)</td>
<td>1 large</td>
<td>0.27</td>
</tr>
<tr>
<td>Almonds</td>
<td>1 ounce</td>
<td>0.23</td>
</tr>
<tr>
<td>Salmon (cooked)</td>
<td>3 ounces*</td>
<td>0.12</td>
</tr>
<tr>
<td>Halibut (broiled)</td>
<td>3 ounces</td>
<td>0.08</td>
</tr>
<tr>
<td>Chicken, light meat (roasted)</td>
<td>3 ounces</td>
<td>0.08</td>
</tr>
<tr>
<td>Chicken, dark meat (roasted)</td>
<td>3 ounces</td>
<td>0.16</td>
</tr>
<tr>
<td>Beef (cooked)</td>
<td>3 ounces</td>
<td>0.16</td>
</tr>
<tr>
<td>Broccoli (boiled)</td>
<td>1/2 cup chopped</td>
<td>0.10</td>
</tr>
<tr>
<td>Asparagus (boiled)</td>
<td>6 spears</td>
<td>0.13</td>
</tr>
<tr>
<td>Spinach (boiled)</td>
<td>1/2 cup</td>
<td>0.21</td>
</tr>
<tr>
<td>Bread, whole wheat</td>
<td>1 slice</td>
<td>0.06</td>
</tr>
<tr>
<td>Bread, white (enriched)</td>
<td>1 slice</td>
<td>0.08</td>
</tr>
</tbody>
</table>

*A 3-ounce serving of meat is about the size of a deck of cards.

**Supplements**

The most common forms of riboflavin available in supplements are riboflavin and riboflavin 5’-monophosphate. Riboflavin is most commonly found in multivitamin and vitamin B-complex preparations (27).

**Safety**

**Toxicity**

No toxic or adverse effects of high riboflavin intake in humans are known. Studies in cell culture indicate that excess riboflavin may increase the risk of DNA strand breaks in the presence of chromium (IV), a known carcinogen (28). This may be of concern to workers exposed to chrome, but no data in humans are available. High-dose riboflavin therapy has been found to intensify urine color to a bright yellow (flavinuria), but this is a harmless side effect. The Food and Nutrition Board did not establish a tolerable upper level of intake (UL) when the RDA was revised in 1998 (1).

**Drug interactions**

Several early reports indicated that women taking high-dose oral contraceptives (OC) had diminished riboflavin nutritional status. However, when investigators controlled for dietary riboflavin intake, no differences between OC users and non-users were found (1). Phenothiazine derivatives like the anti-psychotic medication chlorpromazine and tricyclic antidepressants inhibit the incorporation of riboflavin into FAD and FMN, as do the anti-malarial medication, quinacrine, and the cancer chemotherapy agent, adriamycin (4). Long-term use of the anti-convulsant, phenobarbitol may increase destruction of riboflavin, by liver enzymes, increasing the risk of deficiency (3).
Linus Pauling Institute Recommendation

The RDA for riboflavin (1.3 mg/day for men and 1.1 mg/day for women), which should prevent deficiency in most individuals, is easily met by eating a varied diet. Consuming a varied diet should supply 1.5 mg to 2 mg of riboflavin a day. Following the Linus Pauling Institute recommendation to take a multivitamin/multimineral supplement containing 100% of the Daily Values (DV) will ensure an intake of at least 1.7 mg of riboflavin/day.

Older adults (50 years of age and older)

Some experts in nutrition and aging feel that the RDA (1.3 mg/day for men and 1.1 mg/day for women) leaves little margin for error in people over 50 years of age (29, 30). A recent study of independently living people between 65 and 90 years of age found that almost 25% consumed less than the recommended riboflavin intake, and 10% had biochemical evidence of deficiency (31). Additionally, epidemiological studies of cataract prevalence indicate that riboflavin intakes of 1.6 to 2.2 mg/day may reduce the risk of developing age-related cataracts. Individuals whose diets may not supply adequate riboflavin, especially those over 50, should consider taking a multivitamin/multimineral supplement, which generally provides at least 1.7 mg of riboflavin/day.

References

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http://lpi.oregonstate.edu/infocenter/vitamins/riboflavin/
Thiamin

Thiamin (also spelled thiamine) is a water-soluble B vitamin, previously known as vitamin B₁ or aneurine (1). Isolated and characterized in the 1930s, thiamin was one of the first organic compounds to be recognized as a vitamin (2). Thiamin occurs in the human body as free thiamin and as various phosphorylated forms: thiamin monophosphate (TMP), thiamin triphosphate (TTP), and thiamin pyrophosphate (TPP), which is also known as thiamin diphosphate.

Function

Coenzyme function

Thiamin pyrophosphate (TPP) is a required coenzyme for a small number of very important enzymes. The synthesis of TPP from free thiamin requires magnesium, adenosine triphosphate (ATP), and the enzyme, thiamin pyrophosphokinase.

Pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, and branched chain ketoacid (BCKA) dehydrogenase each comprise a different enzyme complex found within cellular organelles called mitochondria. They catalyze the decarboxylation of pyruvate, α-ketoglutarate, and branched-chain amino acids to form acetyl-coenzyme A, succinyl-coenzyme A, and derivatives of branched chain amino acids, respectively; all products play critical roles in the production of energy from food (2). In addition to the thiamin coenzyme (TPP), each dehydrogenase complex requires a niacin-containing coenzyme (NAD), a riboflavin-containing coenzyme (FAD), and lipoic acid.

Transketolase catalyzes critical reactions in another metabolic pathway known as the pentose phosphate pathway. One of the most important intermediates of this pathway is ribose-5-phosphate, a phosphorylated 5-carbon sugar required for the synthesis of the high-energy ribonucleotides, ATP and guanosine triphosphate (GTP). It is also required for the synthesis of the nucleic acids, DNA and RNA, and the niacin-containing coenzyme NADPH, which is essential for a number of biosynthetic reactions (1, 3). Because transketolase decreases early in thiamin deficiency, measurement of its activity in red blood cells has been used to assess thiamin nutritional status (2).

Deficiency

Beriberi, the disease resulting from severe thiamin deficiency, was described in Chinese literature as early as 2600 B.C. Thiamin deficiency affects the cardiovascular, nervous, muscular, and gastrointestinal systems (2). Beriberi has been termed dry, wet, or cerebral, depending on the systems affected by severe thiamin deficiency (1).

Dry berberi

The main feature of dry (paralytic or nervous) beriberi is peripheral neuropathy. Early in the course of the neuropathy, "burning feet syndrome" may occur. Other symptoms include abnormal (exaggerated) reflexes as well as diminished sensation and weakness in the legs and arms. Muscle pain and tenderness and difficulty
rising from a squatting position have also been observed. Severely thiamin deficient individuals may experience seizures.

**Wet beriberi**

In addition to neurologic symptoms, wet (cardiac) beriberi is characterized by cardiovascular manifestations of thiamin deficiency, which include rapid heart rate, enlargement of the heart, severe swelling (edema), difficulty breathing, and ultimately congestive heart failure.

**Cerebral beriberi**

Cerebral beriberi may lead to Wernicke's encephalopathy and Korsakoff's psychosis, especially in people who abuse alcohol. The diagnosis of Wernicke's encephalopathy is based on a "triad" of signs, which include abnormal eye movements, stance and gait abnormalities, and abnormalities in mental function that may include a confused apathetic state or a profound memory disorder termed Korsakoff's amnesia or Korsakoff's psychosis. Thiamin deficiency affecting the central nervous system is referred to as Wernicke's disease when the amnesic state is not present and Wernicke-Korsakoff syndrome (WKS) when the amnesic symptoms are present along with the eye movement and gait disorders. Most WKS sufferers are alcoholics, although it has been observed in other disorders of gross malnutrition, including stomach cancer and AIDS. Administration of intravenous thiamin to WKS patients generally results in prompt improvement of the eye symptoms, but improvements in motor coordination and memory may be less, depending on how long the symptoms have been present. Recent evidence of increased immune cell activation and increased free radical production in the areas of the brain that are selectively damaged suggests that oxidative stress plays an important role in the neurologic pathology of thiamin deficiency (4).

**Causes of thiamin deficiency**

Thiamin deficiency may result from inadequate thiamin intake, increased requirement for thiamin, excessive loss of thiamin from the body, consumption of anti-thiamin factors in food, or a combination of these factors.

**Inadequate intake**

Inadequate consumption of thiamin is the main cause of thiamin deficiency in underdeveloped countries (2). Thiamin deficiency is common in low-income populations whose diets are high in carbohydrate and low in thiamin (e.g., milled or polished rice). Breast-fed infants whose mothers are thiamin deficient are vulnerable to developing infantile beriberi. Alcoholism, which is associated with low intake of thiamin among other nutrients, is the primary cause of thiamin deficiency in industrialized countries.

**Increased requirement**

Conditions resulting in an increased requirement for thiamin include strenuous physical exertion, fever, pregnancy, breast-feeding, and adolescent growth. Such conditions place individuals with marginal thiamin intake at risk for developing symptomatic thiamin deficiency. Recently, malaria patients in Thailand were found to be severely thiamin deficient more frequently than non-infected individuals (5). Malarial infection leads to a large increase in the metabolic demand for glucose. Because thiamin is required for enzymes involved in
glucose metabolism, the stresses induced by malarial infection could exacerbate thiamin deficiency in predisposed individuals. HIV-infected individuals, whether or not they had developed AIDS, were also found to be at increased risk for thiamin deficiency (6). The lack of association between thiamin intake and evidence of deficiency in these HIV-infected individuals suggests that they had an increased requirement for thiamin. Further, chronic alcohol abuse impairs intestinal absorption and utilization of thiamin (1); thus, alcoholics have increased requirements for thiamin.

**Excessive loss**

Excessive loss of thiamin may precipitate thiamin deficiency. By increasing urinary flow, diuretics may prevent reabsorption of thiamin by the kidneys and increase its excretion in the urine (7, 8), although this remains quite controversial. Individuals with kidney failure requiring hemodialysis lose thiamin at an increased rate and are at risk for thiamin deficiency (9). Alcoholics who maintain a high fluid intake and urine flow rate may also experience increased loss of thiamin, exacerbating the effects of low thiamin intake (10).

**Anti-thiamin factors (ATF)**

The presence of anti-thiamin factors (ATF) in foods also contributes to the risk of thiamin deficiency. Certain plants contain ATF, which react with thiamin to form an oxidized, inactive product. Consuming large amounts of tea and coffee (including decaffeinated), as well as chewing tea leaves and betel nuts, have been associated with thiamin depletion in humans due to the presence of ATF. Thiaminases are enzymes that break down thiamin in food. Individuals who habitually eat certain raw freshwater fish, raw shellfish, and ferns are at higher risk of thiamin deficiency because these foods contain thiaminase that normally is inactivated by heat in cooking (1). In Nigeria, an acute neurologic syndrome (seasonal ataxia) has been associated with thiamin deficiency precipitated by a thiaminase in African silkworms, a traditional high-protein food for some Nigerians (11).

**The Recommended Dietary Allowance (RDA)**

The RDA for thiamin, revised in 1998, was based on the prevention of deficiency in generally healthy individuals (12).

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>0.2 (AI)</td>
<td>0.2 (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
<td>0.3 (AI)</td>
<td>0.3 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Children</td>
<td>4-8 years</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Children</td>
<td>9-13 years</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14-18 years</td>
<td>1.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Adults</td>
<td>19 years and older</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>all ages</td>
<td>-</td>
<td>1.4</td>
</tr>
<tr>
<td>Breastfeeding</td>
<td>all ages</td>
<td>-</td>
<td>1.4</td>
</tr>
</tbody>
</table>
**Disease Prevention**

**Cataracts**

A cross-sectional study of 2,900 Australian men and women, 49 years of age and older, found that those in the highest quintile of thiamin intake were 40% less likely to have nuclear cataracts than those in the lowest quintile (13). In addition, a recent study in 408 U.S. women found that higher dietary intakes of thiamin were inversely associated with five-year change in lens opacification (14). However, these cross-sectional associations have yet to be elucidated by studies of causation.

**Disease Treatment**

**Alzheimer's disease**

Because thiamin deficiency can result in a form of dementia (Wernicke-Korsakoff syndrome), its relationship to Alzheimer's disease and other forms of dementia have been investigated. A case-control study in 38 elderly women found that blood levels of thiamin, thiamin pyrophosphate (TPP), and thiamin monophosphate (TMP) were lower in those with dementia of Alzheimer's type (DAT) compared to the those in the control group (15). Interestingly, several investigators have found evidence of decreased activity of the thiamin pyrophosphate-dependent enzymes, α-ketoglutarate dehydrogenase and transketolase, in the brains of patients who died of Alzheimer's disease (16). Such findings are consistent with evidence of reduced glucose metabolism found on PET scans of the brains of Alzheimer's disease patients (17). The finding of decreased brain levels of TPP in the presence of normal levels of free thiamin and TMP suggests that the decreased enzyme activity is not likely a result of thiamin deficiency but rather of impaired TPP synthesis (18, 19). Presently, there is only slight and inconsistent evidence that thiamin supplements are of benefit in Alzheimer's disease. A double-blind, placebo-controlled study of 15 patients (ten completed the study) reported no beneficial effect of 3 grams of thiamin/day on cognitive decline over a 12-month period. In 1993, a preliminary report from another study claimed a mild benefit of 3 to 8 grams of thiamin/day in DAT, but no additional data from that study are available (20). A mild beneficial effect in patients with Alzheimer's disease was reported after 12 weeks of treatment with 100 milligrams/day of a thiamin derivative (thiamin tetrahydrofurfuryl disulfide), but this study was not placebo-controlled (21). A recent systematic review of randomized, double-blind, placebo-controlled trials of thiamin in patients with DAT found no evidence that thiamin was a useful treatment for the symptoms of Alzheimer's disease (22).

**Congestive heart failure (CHF)**

Severe thiamin deficiency (wet beriberi) can lead to impaired cardiac function and ultimately congestive heart failure (CHF). Although cardiac manifestations of beriberi are rarely encountered in industrialized countries, CHF due to other causes is common, especially in the elderly. Diuretics used in the treatment of CHF, notably furosemide (Lasix), have been found to increase thiamin excretion, potentially leading to marginal thiamin deficiency. A number of studies have examined thiamin nutritional status in CHF patients and most found a fairly low incidence of thiamin deficiency, as measured by assays of transketolase activity. As in the general population, older CHF patients were found to be at higher risk of thiamin deficiency than younger ones (23). An important measure of cardiac function in CHF is the left ventricular ejection fraction (LVEF), which can be assessed by echocardiography. One study in 25 patients found that furosemide use, at doses of 80 mg/day or
greater, was associated with a 98% prevalence of thiamin deficiency (24). In a randomized, double-blind study of 30 CHF patients, all of whom had been taking furosemide (80 mg/day) for at least three months, intravenous (IV) thiamin therapy (200 mg/day) for seven days resulted in an improved LVEF compared to IV placebo (25). When all 30 of the CHF patients in that study subsequently received six weeks of oral thiamin therapy (200 mg/day), the average LVEF improved by 22%. This finding may be relevant because improvements in LVEF have been associated with improved survival in CHF patients (26). However, conclusions from studies published to date are limited due to small sample sizes of the studies, lack of randomization in some studies, and a need for more precise assays of thiamin nutritional status. Presently, the role of thiamin supplementation in maintaining cardiac function in CHF patients remains controversial.

Cancer

Thiamin deficiency has been observed in some cancer patients with rapidly growing tumors. However, research in cell culture and animal models indicates that rapidly dividing cancer cells have a high requirement for thiamin (27). All rapidly dividing cells require nucleic acids at an increased rate, but some cancer cells appear to rely heavily on the TPP-dependent enzyme, transketolase, to provide the ribose-5-phosphate necessary for nucleic acid synthesis. Thiamin supplementation in cancer patients is common to prevent thiamin deficiency, but Boros et al. caution that too much thiamin may actually fuel the growth of some malignant tumors (28), suggesting that thiamin supplementation be reserved for those cancer patients who are actually thiamin deficient. Presently, there is no evidence available from studies in humans to support or refute this theory. However, it would be prudent for individuals with cancer who are considering thiamin supplementation to discuss it with the clinician managing their cancer therapy.

Sources

Food sources

A varied diet should provide most individuals with adequate thiamin to prevent deficiency. In the U.S. the average dietary thiamin intake for young adult men is about 2 mg/day and 1.2 mg/day for young adult women. A survey of people over the age of 60 found an average dietary thiamin intake of 1.4 mg/day for men and 1.1 mg/day for women (12). However, institutionalization and poverty both increase the likelihood of inadequate thiamin intake in the elderly (29). Whole grain cereals, legumes (e.g., beans and lentils), nuts, lean pork, and yeast are rich sources of thiamin (1). Because most of the thiamin is lost during the production of white flour and polished (milled) rice, white rice and foods made from white flour (e.g., bread and pasta) are fortified with thiamin in many Western countries. A number of thiamin-rich foods are listed in the table below along with their thiamin content in milligrams (mg). For more information on the nutrient content of foods, search the USDA food composition database.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Thiamin (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lentils (cooked)</td>
<td>1/2 cup</td>
<td>0.17</td>
</tr>
<tr>
<td>Peas (cooked)</td>
<td>1/2 cup</td>
<td>0.21</td>
</tr>
<tr>
<td>Long grain brown rice (cooked)</td>
<td>1 cup</td>
<td>0.19</td>
</tr>
<tr>
<td>Long grain white rice, enriched (cooked)</td>
<td>1 cup</td>
<td>0.26</td>
</tr>
<tr>
<td>Long grain white rice, unenriched (cooked)</td>
<td>1 cup</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Whole wheat bread 1 slice 0.10
White bread, enriched 1 slice 0.11
Fortified breakfast cereal 1 cup 0.5-2.0
Wheat germ breakfast cereal 1 cup 4.47
Pork, lean (cooked) 3 ounces* 0.72
Brazil nuts 1 ounce 0.18
Pecans 1 ounce 0.19
Spinach (cooked) 1/2 cup 0.09
Orange 1 fruit 0.10
Cantaloupe 1/2 fruit 0.11
Milk 1 cup 0.10
Egg (cooked) 1 large 0.03

*3 ounces of meat is a serving about the size of a deck of cards

Supplements

Thiamin is available in nutritional supplements and for fortification as thiamin hydrochloride and thiamin nitrate (30).

Safety

Toxicity

The Food and Nutrition Board did not set a tolerable upper level (UL) of intake for thiamin because there are no well-established toxic effects from the consumption of excess thiamin in food or through long-term oral supplementation (up to 200 mg/day). A small number of life threatening anaphylactic reactions have been observed with large intravenous doses of thiamin (12).

Drug interactions

Reduced blood levels of thiamin have been reported in individuals with seizure disorders (epilepsy) taking the anticonvulsant medication, phenytoin, for long periods of time (31). 5-Fluorouracil, a drug used in cancer therapy, inhibits the phosphorylation of thiamin to thiamin pyrophosphate (TPP) (32). Diuretics, especially furosemide (Lasix), may increase the risk of thiamin deficiency in individuals with marginal thiamin intake due to increased urinary excretion of thiamin (8). Moreover, chronic alcohol abuse is associated with thiamin deficiency due to low dietary intake, impaired absorption and utilization, and increased excretion of the vitamin (1).

Linus Pauling Institute Recommendation

The Linus Pauling Institute supports the recommendation by the Food and Nutrition Board of 1.2 mg of thiamin/day for men and 1.1 mg/day for women. A varied diet should provide enough thiamin for most people.
Following the Linus Pauling Institute recommendation to take a daily multivitamin/multimineral supplement, containing 100% of the Daily Values (DV), will ensure an intake of at least 1.5 mg of thiamin/day.

**Older adults (65 years and older)**

Presently, there is no evidence that the requirement for thiamin is increased in older adults, but some studies have found inadequate dietary intake and thiamin insufficiency to be more common in elderly populations (29). Thus, it would be prudent for older adults to take a multivitamin/multimineral supplement, which will generally provide at least 1.5 mg of thiamin/day.

**References**

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http://lpi.oregonstate.edu/infocenter/vitamins/thiamin/
**Vitamin B\textsubscript{6}**

Vitamin B\textsubscript{6} is a water-soluble vitamin that was first isolated in the 1930s. There are three traditionally considered forms of vitamin B\textsubscript{6}: pyridoxal (PL), pyridoxine (PN), pyridoxamine (PM). The phosphate ester derivative pyridoxal 5’-phosphate (PLP) is the principal coenzyme form and has the most importance in human metabolism (1-3).

**Function**

Vitamin B\textsubscript{6} must be obtained from the diet because humans cannot synthesize it. PLP plays a vital role in the function of approximately 100 enzymes that catalyze essential chemical reactions in the human body (1-5). For example, PLP functions as a coenzyme for glycogen phosphorylase, an enzyme that catalyzes the release of glucose from stored glycogen. Much of the PLP in the human body is found in muscle bound to glycogen phosphorylase. PLP is also a coenzyme for reactions used to generate glucose from amino acids, a process known as gluconeogenesis (4, 5).

**Nervous system function**

In the brain, the synthesis of the neurotransmitter, serotonin, from the amino acid, tryptophan, is catalyzed by a PLP-dependent enzyme. Other neurotransmitters, such as dopamine, norepinephrine and gamma-aminobutyric acid (GABA), are also synthesized using PLP-dependent enzymes (4).

**Red blood cell formation and function**

PLP functions as a coenzyme in the synthesis of heme, an iron-containing component of hemoglobin. Hemoglobin is found in red blood cells and is critical to their ability to transport oxygen throughout the body. Both PL and PLP are able to bind to the hemoglobin molecule and affect its ability to pick up and release oxygen. However, the impact of this on normal oxygen delivery to tissues is not known (4).

**Niacin formation**

The human requirement for another B vitamin, niacin, can be met in part by the conversion of the essential amino acid, tryptophan, to niacin, as well as through dietary intake. PLP is a coenzyme for a critical reaction in the synthesis of niacin from tryptophan; thus, adequate vitamin B\textsubscript{6} decreases the requirement for dietary niacin (4).

**Hormone function**

Steroid hormones, such as estrogen and testosterone, exert their effects in the body by binding to steroid hormone receptors in the nucleus of the cell and altering gene transcription. PLP binds to steroid receptors in a manner that inhibits the binding of steroid hormones, thus decreasing their effects. The binding of PLP to steroid receptors for estrogen, progesterone, testosterone, and other steroid hormones suggests that the vitamin B\textsubscript{6} status of an individual may have implications for diseases affected by steroid hormones, including breast cancer and prostate cancers (4).
Nucleic acid synthesis

PLP serves as a coenzyme for a key enzyme involved in the mobilization of single-carbon functional groups (one-carbon metabolism). Such reactions are involved in the synthesis of nucleic acids. The effect of vitamin B₆ deficiency on the function of the immune system may be partly related to the role of PLP in one-carbon metabolism (see Disease Prevention).

Deficiency

Severe deficiency of vitamin B₆ is uncommon. Alcoholics are thought to be most at risk of vitamin B₆ deficiency due to low dietary intakes and impaired metabolism of the vitamin. In the early 1950s, seizures were observed in infants as a result of severe vitamin B₆ deficiency caused by an error in the manufacture of infant formula. Abnormal electroencephalogram (EEG) patterns have been noted in some studies of vitamin B₆ deficiency. Other neurologic symptoms noted in severe vitamin B₆ deficiency include irritability, depression, and confusion; additional symptoms include inflammation of the tongue, sores or ulcers of the mouth, and ulcers of the skin at the corners of the mouth (2).

The Recommended Dietary Allowance (RDA)

Because vitamin B₆ is involved in many aspects of metabolism, several factors are likely to effect an individual's requirement for vitamin B₆. Of those factors, protein intake has been the most studied. Increased dietary protein results in an increased requirement for vitamin B₆, probably because PLP is a coenzyme for many enzymes involved in amino acid metabolism (6). Unlike previous recommendations, the Food and Nutrition Board (FNB) of the Institute of Medicine did not express the most recent RDA for vitamin B₆ in terms of protein intake, although the relationship was considered in setting the RDA (7). The current RDA was revised by the Food and Nutrition Board (FNB) in 1998 and is presented in the table below.

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males (mg/day)</th>
<th>Females (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>0.1 (AI)</td>
<td>0.1 (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
<td>0.3 (AI)</td>
<td>0.3 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Children</td>
<td>4-8 years</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Children</td>
<td>9-13 years</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14-18 years</td>
<td>1.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Adults</td>
<td>19-50 years</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Adults</td>
<td>51 years and older</td>
<td>1.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>all ages</td>
<td>-</td>
<td>1.9</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>all ages</td>
<td>-</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Disease Prevention

Homocysteine and cardiovascular disease

Even moderately elevated levels of homocysteine in the blood have been associated with increased risk for cardiovascular disease, including heart disease and stroke (8). During protein digestion, amino acids, including methionine, are released. Homocysteine is an intermediate in the metabolism of methionine. Healthy individuals utilize two different pathways to metabolize homocysteine. One pathway converts homocysteine back to methionine and is dependent on folic acid and vitamin B12. The other pathway converts homocysteine to the amino acid cysteine and requires two vitamin B6(PLP)-dependent enzymes. Thus, the amount of homocysteine in the blood is regulated by at least three vitamins: folic acid, vitamin B12, and vitamin B6 (diagram). Several large observational studies have demonstrated an association between low vitamin B6 intake or status with increased blood homocysteine levels and increased risk of cardiovascular diseases. A large prospective study found the risk of heart disease in women who consumed, on average, 4.6 mg of vitamin B6 daily was only 67% of the risk in women who consumed an average of 1.1 mg daily (9). Another large prospective study found higher plasma levels of PLP were associated with a decreased risk of cardiovascular disease independent of homocysteine levels (10). Further, several studies have reported that low plasma PLP status is a risk factor for coronary artery disease (11-13). In contrast to folic acid supplementation, studies supplementing individuals with only vitamin B6 have not resulted in significant decreases in basal (fasting) levels of homocysteine. However, one study found that vitamin B6 supplementation was effective in lowering blood homocysteine levels after an oral dose of methionine (methionine load test) was given (14), suggesting vitamin B6 may play a role in the metabolism of homocysteine after meals.

Immune function

Low vitamin B6 intake and nutritional status have been associated with impaired immune function, especially in the elderly. Decreased production of immune system cells known as lymphocytes, as well as decreased production of an important immune system protein called interleukin-2, have been reported in vitamin B6 deficient individuals (15). Restoration of vitamin B6 status has resulted in normalization of lymphocyte proliferation and interleukin-2 production, suggesting that adequate vitamin B6 intake is important for optimal immune system function in older individuals (15, 16). However, one study found that the amount of vitamin B6 required to reverse these immune system impairments in the elderly was 2.9 mg/day for men and 1.9 mg/day for women; these vitamin B6 requirements are higher than the current RDA (15).

Cognitive function

A few studies have associated cognitive decline in the elderly or Alzheimer's disease with inadequate nutritional status of folic acid, vitamin B12, and vitamin B6 and thus, elevated levels of homocysteine (17). One observational study found that higher plasma vitamin B6 levels were associated with better performance on two measures of memory, but plasma vitamin B6 levels were unrelated to performance on 18 other cognitive tests (18). Similarly, a double-blind, placebo-controlled study in 38 healthy elderly men found that vitamin B6 supplementation improved memory but had no effect on mood or mental performance (19). Further, a placebo-controlled trial in 211 healthy younger, middle-aged, and older women found that vitamin B6 supplementation (75 mg/day) for five weeks improved memory performance in some age groups but had no effect on mood (20). Recently, a systematic review of randomized trials concluded that there is inadequate evidence that supplementation with vitamin B6, vitamin B12, or folic acid improves cognition in those with normal or impaired
cognitive function (21). Because of mixed findings, it is presently unclear whether supplementation with B vitamins might blunt cognitive decline in the elderly. Further, it is not known if marginal B vitamin deficiencies, which are relatively common in the elderly, even contribute to age-associated declines in cognitive function, or whether both result from processes associated with aging and/or disease.

**Kidney stones**

A large prospective study examined the relationship between vitamin B$_6$ intake and the occurrence of symptomatic kidney stones in women. A group of more than 85,000 women without a prior history of kidney stones were followed over 14 years and those who consumed 40 mg or more of vitamin B$_6$ daily had only two thirds the risk of developing kidney stones compared with those who consumed 3 mg or less (22). However, in a group of more than 45,000 men followed over six years, no association was found between vitamin B$_6$ intake and the occurrence of kidney stones (23). Limited data have shown that supplementation of vitamin B$_6$ at levels higher than the tolerable upper intake level (100 mg/day) decreases elevated urinary oxalate levels, an important determinant of calcium oxalate kidney stone formation in some individuals. However, it is less clear that supplementation actually resulted in decreased formation of calcium oxalate kidney stones. Presently, the relationship between vitamin B$_6$ intake and the risk of developing kidney stones requires further study before any recommendations can be made.

**Disease Treatment**

Vitamin B$_6$ supplements at pharmacologic doses (i.e., doses much larger than those needed to prevent deficiency) have been used in an attempt to treat a wide variety of conditions, some of which are discussed below. In general, well designed, placebo-controlled studies have shown little evidence that large supplemental doses of vitamin B$_6$ are beneficial (24).

**Side effects of oral contraceptives**

Because vitamin B$_6$ is required for the metabolism of the amino acid tryptophan, the tryptophan load test (an assay of tryptophan metabolites after an oral dose of tryptophan) was used as a functional assessment of vitamin B$_6$ status. Abnormal tryptophan load tests in women taking high-dose oral contraceptives in the 1960s and 1970s suggested that these women were vitamin B$_6$ deficient. Abnormal results in the tryptophan load test led a number of clinicians to prescribe high doses (100-150 mg/day) of vitamin B$_6$ to women in order to relieve depression and other side effects sometimes experienced with oral contraceptives. However, most other indices of vitamin B$_6$ status were normal in women on high-dose oral contraceptives, and it is unlikely that the abnormality in tryptophan metabolism was due to vitamin B$_6$ deficiency (24). A more recent placebo-controlled study in women on the lower dose oral contraceptives, which are commonly prescribed today, found that doses up to 150 mg/day of vitamin B$_6$ (pyridoxine) had no benefit in preventing side effects, such as nausea, vomiting, dizziness, depression, and irritability (25).

**Premenstrual syndrome (PMS)**

The use of vitamin B$_6$ to relieve the side effects of high-dose oral contraceptives led to the use of vitamin B$_6$ in the treatment of premenstrual syndrome (PMS). PMS refers to a cluster of symptoms, including but not limited to fatigue, irritability, moodiness/depression, fluid retention, and breast tenderness, that begin sometime after
ovulation (mid-cycle) and subside with the onset of menstruation (the monthly period). A review of 12 placebo-controlled double-blind trials on vitamin B₆ use for PMS treatment concluded that evidence for a beneficial effect was weak (26). A more recent review of 25 studies suggested that supplemental vitamin B₆, up to 100 mg/day, may be of value to treat PMS; however, only limited conclusions could be drawn because most of the studies were of poor quality (27).

Depression

Because a key enzyme in the synthesis of the neurotransmitters serotonin and norepinephrine is PLP-dependent, it has been suggested that vitamin B₆ deficiency may lead to depression. However, clinical trials have not provided convincing evidence that vitamin B₆ supplementation is an effective treatment for depression (24, 28), though vitamin B₆ may have therapeutic efficacy in premenopausal women (28).

Morning sickness (nausea and vomiting in pregnancy)

Vitamin B₆ has been used since the 1940s to treat nausea during pregnancy. Vitamin B₆ was included in the medication Bendectin, which was prescribed for the treatment of morning sickness and later withdrawn from the market due to unproven concerns that it increased the risk of birth defects. Vitamin B₆ itself is considered safe during pregnancy and has been used in pregnant women without any evidence of fetal harm (29). The results of two double-blind, placebo-controlled trials that used 25 mg of pyridoxine every eight hours for three days (30) or 10 mg of pyridoxine every eight hours for five days (29) suggest that vitamin B₆ may be beneficial in alleviating morning sickness. Each study found a slight but significant reduction in nausea or vomiting in pregnant women. A recent systematic review of placebo-controlled trials on nausea during early pregnancy found vitamin B₆ to be somewhat effective (31). However, it should be noted that morning sickness also resolves without any treatment, making it difficult to perform well-controlled trials.

Carpal tunnel syndrome

Carpal tunnel syndrome causes numbness, pain, and weakness of the hand and fingers due to compression of the median nerve at the wrist. It may result from repetitive stress injury of the wrist or from soft tissue swelling, which sometimes occurs with pregnancy or hypothyroidism. Several early studies by the same investigator suggested that vitamin B₆ status was low in individuals with carpal tunnel syndrome and that supplementation with 100-200 mg/day over several months was beneficial (32, 33). A recent study in men not taking vitamin supplements found that decreased blood levels of PLP were associated with increased pain, tingling, and nocturnal wakening, all symptoms of carpal tunnel syndrome (34). Studies using electrophysiological measurements of median nerve conduction have largely failed to find an association between vitamin B₆ deficiency and carpal tunnel syndrome. While a few trials have noted some symptomatic relief with vitamin B₆ supplementation, double-blind, placebo-controlled trials have not generally found vitamin B₆ to be effective in treating carpal tunnel syndrome (24, 35).

Sources

Food sources
Surveys in the U.S. have shown that dietary intake of vitamin B₆ averages about 2 mg/day for men and 1.5 mg/day for women. A survey of elderly individuals found that men and women over 60 years old consumed about 1.2 mg/day and 1.0 mg/day, respectively; both intakes are lower than the current RDA. Certain plant foods contain a unique form of vitamin B₆ called pyridoxine glucoside; this form of vitamin B₆ appears to be only about half as bioavailable as vitamin B₆ from other food sources or supplements. Vitamin B₆ in a mixed diet has been found to be approximately 75% bioavailable (7). In most cases, including foods in the diet that are rich in vitamin B₆ should supply enough to prevent deficiency. However, those who follow a very restricted vegetarian diet might need to increase their vitamin B₆ intake by eating foods fortified with vitamin B₆ or by taking a supplement. Some foods that are relatively rich in vitamin B₆ and their vitamin B₆ content in milligrams (mg) are listed in the table below. For more information on the nutrient content of specific foods, search the USDA food composition database.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Vitamin B₆ (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fortified cereal</td>
<td>1 cup</td>
<td>0.5-2.5</td>
</tr>
<tr>
<td>Banana</td>
<td>1 medium</td>
<td>0.43</td>
</tr>
<tr>
<td>Salmon, wild, cooked</td>
<td>3 ounces*</td>
<td>0.48</td>
</tr>
<tr>
<td>Turkey, without skin, cooked</td>
<td>3 ounces</td>
<td>0.39</td>
</tr>
<tr>
<td>Chicken, light meat without skin, cooked</td>
<td>3 ounces</td>
<td>0.51</td>
</tr>
<tr>
<td>Potato, Russet, baked, with skin</td>
<td>1 medium</td>
<td>0.70</td>
</tr>
<tr>
<td>Spinach, cooked</td>
<td>1 cup</td>
<td>0.44</td>
</tr>
<tr>
<td>Hazelnuts, dry roasted</td>
<td>1 ounce</td>
<td>0.18</td>
</tr>
<tr>
<td>Vegetable juice cocktail</td>
<td>6 ounces</td>
<td>0.26</td>
</tr>
</tbody>
</table>

* A 3-ounce serving of meat or fish is about the size of a deck of cards.

**Supplements**

Vitamin B₆ is available as pyridoxine hydrochloride in multivitamin, vitamin B-complex, and vitamin B₆ supplements (36).

**Safety**

**Toxicity**

Because adverse effects have only been documented from vitamin B₆ supplements and never from food sources, safety concerning only the supplemental form of vitamin B₆ (pyridoxine) is discussed. Although vitamin B₆ is a water-soluble vitamin and is excreted in the urine, long-term supplementation with very high doses of pyridoxine may result in painful neurological symptoms known as sensory neuropathy. Symptoms include pain and numbness of the extremities and in severe cases, difficulty walking. Sensory neuropathy typically develops at doses of pyridoxine in excess of 1,000 mg per day. However, there have been a few case reports of individuals who developed sensory neuropathies at doses of less than 500 mg daily over a period of months. Yet, none of the studies in which an objective neurological examination was performed reported evidence of
sensory nerve damage at intakes below 200 mg pyridoxine daily (24). To prevent sensory neuropathy in virtually all individuals, the Food and Nutrition Board of the Institute of Medicine set the tolerable upper intake level (UL) for pyridoxine at 100 mg/day for adults (see table below) (7). Because placebo-controlled studies have generally failed to show therapeutic benefits of high doses of pyridoxine, there is little reason to exceed the UL of 100 mg/day.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>UL (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants 0-12 months</td>
<td>Not possible to establish*</td>
</tr>
<tr>
<td>Children 1-3 years</td>
<td>30</td>
</tr>
<tr>
<td>Children 4-8 years</td>
<td>40</td>
</tr>
<tr>
<td>Children 9-13 years</td>
<td>60</td>
</tr>
<tr>
<td>Adolescents 14-18 years</td>
<td>80</td>
</tr>
<tr>
<td>Adults 19 years and older</td>
<td>100</td>
</tr>
</tbody>
</table>

*Source of intake should be from food and formula only.

**Drug interactions**

Certain medications interfere with the metabolism of vitamin B₆; therefore, some individuals may be vulnerable to a vitamin B₆ deficiency if supplemental vitamin B₆ is not taken. Anti-tuberculosis medications, including isoniazid and cycloserine, the metal chelator penicillamine, and antiparkinsonian drugs including L-dopa, all form complexes with vitamin B₆ and thus create a functional deficiency. Additionally, the efficacy of other medications may be altered by high doses of vitamin B₆. For instance, high doses of vitamin B₆ have been found to decrease the efficacy of two anticonvulsants, phenobarbital and phenytoin, as well as L-dopa (4, 24).

**Linus Pauling Institute Recommendation**

Metabolic studies suggest that young women require 0.02 mg of vitamin B₆ per gram of protein consumed daily (6, 37, 38). Using the upper boundary for acceptable levels of protein intake for women (100 grams/day), the daily vitamin B₆ requirement for young women would be calculated at 2.0 mg daily. Older adults may also require at least 2.0 mg/day. For these reasons, the Linus Pauling Institute recommends that all adults consume at least 2.0 mg of vitamin B₆ daily. Following the Linus Pauling Institute recommendation to take a daily multivitamin-mineral supplement containing 100% of the Daily Value for vitamin B₆ will ensure an intake of at least 2.0 mg/day of vitamin B₆. Although a vitamin B₆ intake of 2.0 mg daily is slightly higher than the most recent RDA, it is 50 times less than the tolerable upper intake level (UL) set by the Food and Nutrition Board (see Safety).

**Older adults (65 years and older)**

Metabolic studies have indicated that the requirement for vitamin B₆ in older adults is approximately 2.0 mg daily (39); this requirement could be even higher if the effect of marginally deficient vitamin B₆ intakes on immune function and homocysteine levels are clarified. Despite evidence that the requirement for vitamin B₆
may be slightly higher in older adults, several surveys have found that over half of individuals over age 60 consume less than the current RDA (1.7 mg/day for men and 1.5 mg/day for women). For these reasons, the Linus Pauling Institute recommends that older adults take a multivitamin/multimineral supplement, which generally provides at least 2.0 mg of vitamin B₆ daily.

References

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http://lpi.oregonstate.edu/infocenter/vitamins/vitaminB6/
**Vitamin B₁₂**

Vitamin B₁₂ has the largest and most complex chemical structure of all the vitamins. It is unique among vitamins in that it contains a metal ion, cobalt. For this reason *cobalamin* is the term used to refer to compounds having vitamin B₁₂ activity. Methylcobalamin and 5-deoxyadenosyl cobalamin are the forms of vitamin B₁₂ used in the human body (1). The form of cobalamin used in most supplements, cyanocobalamin, is readily converted to 5-deoxyadenosyl and methylcobalamin in the body. In mammals, cobalamin is a cofactor for only two enzymes, methionine synthase and L-methylmalonyl-CoA mutase (2).

**Function**

**Cofactor for methionine synthase**

Methylcobalamin is required for the function of the folate-dependent enzyme, methionine synthase. This enzyme is required for the synthesis of the amino acid, methionine, from homocysteine. Methionine in turn is required for the synthesis of S-adenosylmethionine, a methyl group donor used in many biological methylation reactions, including the methylation of a number of sites within DNA and RNA (3). Methylation of DNA may be important in cancer prevention. Inadequate function of methionine synthase can lead to an accumulation of homocysteine, which has been associated with increased risk of cardiovascular diseases (diagram).

**Cofactor for L-methylmalonyl-CoA mutase**

5-Deoxyadenosylcobalamin is required by the enzyme that catalyzes the conversion of L-methylmalonyl-CoA to succinyl-CoA. This biochemical reaction plays an important role in the production of energy from fats and proteins. Succinyl CoA is also required for the synthesis of hemoglobin, the oxygen carrying pigment in red blood cells (3).

**Deficiency**

Vitamin B₁₂ deficiency is estimated to affect 10%-15% of individuals over the age of 60 (4). Absorption of vitamin B₁₂ from food requires normal function of the stomach, pancreas, and small intestine. Stomach acid and enzymes free vitamin B₁₂ from food, allowing it to bind to other proteins called R proteins (3). In the alkaline environment of the small intestine, R proteins are degraded by pancreatic enzymes, freeing vitamin B₁₂ to bind to intrinsic factor (IF), a protein secreted by specialized cells in the stomach. Receptors on the surface of the small intestine take up the IF-B₁₂ complex only in the presence of calcium, which is supplied by the pancreas (5). Vitamin B₁₂ can also be absorbed by passive diffusion, but this process is very inefficient—only about 1% absorption of the vitamin B₁₂ dose is absorbed passively (2).

**Causes of vitamin B₁₂ deficiency**

The most common causes of vitamin B₁₂ deficiency are: 1) an autoimmune condition known as pernicious anemia and 2) food-bound vitamin B₁₂ malabsorption. Although both causes become more common with increasing age, they are separate conditions (4).

**Pernicious anemia**
Pernicious anemia has been estimated to be present in approximately 2% of individuals over 60 (6). Although anemia is often a symptom, the condition is actually the end stage of an autoimmune inflammation of the stomach, resulting in destruction of stomach cells by one's own antibodies. Progressive destruction of the cells that line the stomach causes decreased secretion of acid and enzymes required to release food-bound vitamin B$_{12}$. Antibodies to intrinsic factor (IF) bind to IF preventing formation of the IF-B$_{12}$ complex, further inhibiting vitamin B$_{12}$ absorption. If the body's vitamin B$_{12}$ stores are adequate prior to the onset of pernicious anemia, it may take years for symptoms of deficiency to develop. About 20% of the relatives of pernicious anemia patients also have pernicious anemia, suggesting a genetic predisposition. Treatment of pernicious anemia generally requires injections of vitamin B$_{12}$ to bypass intestinal absorption. High-dose oral supplementation is another treatment option, because consuming 1,000 mcg (1 mg)/day of vitamin B$_{12}$ orally should result in the absorption of about 10 mcg/day (1% of dose) by passive diffusion (4). In fact, high-dose oral therapy is considered to be as effective as intramuscular injection (7-10).

**Food-bound vitamin B$_{12}$ malabsorption**

Food-bound vitamin B$_{12}$ malabsorption is defined as an impaired ability to absorb food or protein-bound vitamin B$_{12}$, although the free form is fully absorbable (11). In the elderly, food-bound vitamin B$_{12}$ malabsorption is thought to result mainly from atrophic gastritis, a chronic inflammation of the lining of the stomach that ultimately results in the loss of glands in the stomach (atrophy) and decreased stomach acid production. Because stomach acid is required for the release of vitamin B$_{12}$ from the proteins in food, vitamin B$_{12}$ absorption is diminished. Decreased stomach acid production also provides an environment conducive to the overgrowth of anaerobic bacteria in the stomach, which further interferes with vitamin B$_{12}$ absorption (3). Because vitamin B$_{12}$ in supplements is not bound to protein, and because intrinsic factor (IF) is still available, the absorption of supplemental vitamin B$_{12}$ is not reduced as it is in pernicious anemia. Thus, individuals with food-bound vitamin B$_{12}$ malabsorption do not have an increased requirement for vitamin B$_{12}$; they simply need it in the crystalline form found in fortified foods and dietary supplements.

**Atrophic gastritis**

Atrophic gastritis is thought to affect 10%-30% of people over 60 years of age, and the condition is frequently associated with infection by the bacteria, Helicobacter pylori. H. pylori infection induces chronic inflammation of the stomach, which may progress to peptic ulcer disease, atrophic gastritis, and/or gastric cancer in some individuals. The relationship of H. pylori infection to atrophic gastritis, gastric cancer, and vitamin B$_{12}$ deficiency is presently an area of active research (4).

**Other causes of vitamin B$_{12}$ deficiency**

Other causes of vitamin B$_{12}$ deficiency include surgical resection of the stomach or portions of the small intestine where receptors for the IF-B$_{12}$ complex are located. Conditions affecting the small intestine, such as malabsorption syndromes (celiac disease and tropical sprue), may also result in vitamin B$_{12}$ deficiency. Because the pancreas provides critical enzymes as well as calcium required for vitamin B$_{12}$ absorption, pancreatic insufficiency may contribute to B$_{12}$ deficiency. Since vitamin B$_{12}$ is found only in foods of animal origin, a strict vegetarian (vegan) diet has resulted in cases of vitamin B$_{12}$ deficiency. Alcoholics may experience reduced intestinal absorption of vitamin B$_{12}$ (2). Individuals with acquired immunodeficiency syndrome (AIDS) appear to be at increased risk of deficiency, possibly related to a failure of the IF-B$_{12}$ receptor to take up the IF-B$_{12}$
complex (3). Long-term use of acid-reducing drugs has also been implicated in vitamin B<sub>12</sub> deficiency (see Drug interactions).

**Symptoms of vitamin B<sub>12</sub> deficiency**

Vitamin B<sub>12</sub> deficiency results in impairment of the activities of B<sub>12</sub>-requiring enzymes. Impaired activity of methionine synthase may result in elevated homocysteine levels, while impaired activity of L-methylmalonyl-CoA mutase results in increased levels of a metabolite of methylmalonyl-CoA called methylmalonic acid (MMA). Individuals with mild vitamin B<sub>12</sub> deficiency may not experience symptoms, although blood levels of homocysteine and/or MMA may be elevated (12).

**Megaloblastic anemia**

Diminished activity of methionine synthase in vitamin B<sub>12</sub> deficiency inhibits the regeneration of tetrahydrofolate (THF) and traps folate in a form that is not usable by the body (diagram), resulting in symptoms of folate deficiency even in the presence of adequate folate levels. Thus, in both folate and vitamin B<sub>12</sub> deficiencies, folate is unavailable to participate in DNA synthesis. This impairment of DNA synthesis affects the rapidly dividing cells of the bone marrow earlier than other cells, resulting in the production of large, immature, hemoglobin-poor red blood cells. The resulting anemia is known as megaloblastic anemia and is the symptom for which the disease, pernicious anemia, was named (3). Supplementation with folic acid will provide enough usable folate to restore normal red blood cell formation. However, if vitamin B<sub>12</sub> deficiency is the cause, it will persist despite the resolution of the anemia. Thus, megaloblastic anemia should not be treated with folic acid until the underlying cause has been determined (5).

**Neurologic symptoms**

The neurologic symptoms of vitamin B<sub>12</sub> deficiency include numbness and tingling of the arms and, more commonly, the legs, difficulty walking, memory loss, disorientation, and dementia with or without mood changes. Although the progression of neurologic complications is generally gradual, such symptoms are not always reversible with treatment of vitamin B<sub>12</sub> deficiency, especially if they have been present for a long time. Neurologic complications are not always associated with megaloblastic anemia and are the only clinical symptom of vitamin B<sub>12</sub> deficiency in about 25% of cases (6). Although vitamin B<sub>12</sub> deficiency is known to damage the myelin sheath covering cranial, spinal, and peripheral nerves, the biochemical processes leading to neurological damage in B<sub>12</sub> deficiency are not well understood (3).

**Gastrointestinal symptoms**

Tongue soreness, appetite loss, and constipation have also been associated with vitamin B<sub>12</sub> deficiency. The origins of these symptoms are unclear, but they may be related to the stomach inflammation underlying some cases of B<sub>12</sub> deficiency, or to the increased vulnerability of rapidly dividing gastrointestinal cells to impaired DNA synthesis (6).

**The Recommended Dietary Allowance (RDA)**


The current RDA was revised by the Food and Nutrition Board (FNB) of the Institute of Medicine in 1998. Because of the increased risk of food-bound vitamin B$_{12}$ malabsorption in older adults, the FNB recommended that adults over 50 years of age get most of the RDA from fortified food or vitamin B$_{12}$-containing supplements (6).

### Recommended Dietary Allowance (RDA) for Vitamin B$_{12}$

<table>
<thead>
<tr>
<th>Life Stage</th>
<th>Age</th>
<th>Males (mcg/day)</th>
<th>Females (mcg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>0-6 months</td>
<td>0.4 (AI)</td>
<td>0.4 (AI)</td>
</tr>
<tr>
<td>Infants</td>
<td>7-12 months</td>
<td>0.5 (AI)</td>
<td>0.5 (AI)</td>
</tr>
<tr>
<td>Children</td>
<td>1-3 years</td>
<td>0.9</td>
<td>0.9</td>
</tr>
<tr>
<td>Children</td>
<td>4-8 years</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>Children</td>
<td>9-13 years</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Adolescents</td>
<td>14-18 years</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Adults</td>
<td>19-50 years</td>
<td>2.4</td>
<td>2.4</td>
</tr>
<tr>
<td>Adults</td>
<td>51 years and older</td>
<td>2.4*</td>
<td>2.4*</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>all ages</td>
<td>-</td>
<td>2.6</td>
</tr>
<tr>
<td>Breast-feeding</td>
<td>all ages</td>
<td>-</td>
<td>2.8</td>
</tr>
</tbody>
</table>

*Vitamin B$_{12}$ intake should be from supplements or fortified foods due to the age-related increase in food bound malabsorption.

### Disease Prevention

#### Homocysteine and cardiovascular disease

The results of more than 80 studies indicate that even moderately elevated levels of homocysteine in the blood increase the risk of cardiovascular diseases (13), though the mechanism by which homocysteine increases the disease risk remains the subject of a great deal of research. The amount of homocysteine in the blood is regulated by at least three vitamins: folate, vitamin B$_{12}$, and vitamin B$_{6}$ (diagram). Analysis of the results of 12 homocysteine-lowering trials showed folic acid supplementation (0.5-5 mg/day) had the greatest lowering effect on blood homocysteine levels (25% decrease); co-supplementation with folic acid and vitamin B$_{12}$ (mean 0.5 mg/day or 500 mcg/day) provided an additional 7% reduction (32% decrease) in blood homocysteine concentrations (14). The results of a sequential supplementation trial in 53 men and women indicated that after folic acid supplementation, vitamin B$_{12}$ became the major determinant of plasma homocysteine levels (15). Some evidence indicates that vitamin B$_{12}$ deficiency is a major cause of elevated homocysteine levels in people over the age of 60. Two studies found blood methylmalonic acid (MMA) levels to be elevated in more than 60% of elderly individuals with elevated homocysteine levels. An elevated MMA level in conjunction with elevated homocysteine, in the absence of impaired kidney function, suggests either a vitamin B$_{12}$ deficiency or a combined B$_{12}$ and folate deficiency (16). Thus, it is important to evaluate vitamin B$_{12}$ status as well as kidney function in older individuals with elevated homocysteine levels prior to initiating homocysteine-lowering therapy. For more information regarding homocysteine and cardiovascular diseases, see the article on folic acid.
Although increased intake of folic acid and vitamin B<sub>12</sub> has been found to decrease homocysteine levels, it is not presently known whether increasing intake of these vitamins will translate to reductions in risk for cardiovascular diseases. However, several randomized placebo-controlled trials are presently being conducted to determine whether homocysteine lowering through folic acid and other B vitamin supplementation reduces the incidence of cardiovascular diseases. A meta-analysis of data from four of the ongoing trials shows that B vitamin supplementation had no significant effect on risk of coronary heart disease or stroke, but only about 14,000 participants were included in analysis and thus any conclusions are limited (17). Nevertheless, the completion of ongoing clinical trials should help to answer whether or not supplemental B vitamins lower risk for cardiovascular diseases.

**Cancer**

Folate is required for synthesis of DNA, and there is evidence that decreased availability of folate results in strands of DNA that are more susceptible to damage. Deficiency of vitamin B<sub>12</sub> traps folate in a form that is unusable by the body for DNA synthesis. Both vitamin B<sub>12</sub> and folate deficiencies result in a diminished capacity for methylation reactions (diagram). Thus, vitamin B<sub>12</sub> deficiency may lead to an elevated rate of DNA damage and altered methylation of DNA, both of which are important risk factors for cancer. A recent series of studies in young adults and older men indicated that increased levels of homocysteine and decreased levels of vitamin B<sub>12</sub> in the blood were associated with a biomarker of chromosome breakage in white blood cells. In a double-blind, placebo-controlled study, the same biomarker of chromosome breakage was minimized in young adults who were supplemented with 700 mcg of folic acid and 7 mcg of vitamin B<sub>12</sub> daily in cereal for two months (18).

**Breast cancer**

A case-control study compared prediagnostic levels of serum folate, vitamin B<sub>6</sub>, and vitamin B<sub>12</sub> in 195 women later diagnosed with breast cancer and 195 age-matched women who were not diagnosed with breast cancer (19). Among women who were postmenopausal at the time of blood donation, the association between blood levels of vitamin B<sub>12</sub> and breast cancer suggested a threshold effect. The risk of breast cancer was more than doubled in women with serum vitamin B<sub>12</sub> levels in the lowest quintile (1/5) compared to women in the four highest quintiles. The investigators found no relationship between breast cancer and serum levels of vitamin B<sub>6</sub>, folate, or homocysteine. A case-control study in Mexican women (475 cases and 1,391 controls) reported that breast cancer risk for women in the highest quartile (1/4) of vitamin B<sub>12</sub> intake was 68% lower than those in the lowest quartile (20). Stratification of the data revealed that the inverse association between dietary vitamin B<sub>12</sub> intake and breast cancer risk was stronger in postmenopausal women compared to premenopausal women, though both associations were statistically significant. Because these studies were observational, it cannot be determined whether decreased serum levels of vitamin B<sub>12</sub> or low dietary vitamin B<sub>12</sub> intakes were a cause or a result of breast cancer. Previously, there has been little evidence to suggest a relationship between vitamin B<sub>12</sub> status and breast cancer risk. However, high dietary folate intakes have been associated with reduced risk for breast cancer in several studies, and some studies have reported that vitamin B<sub>12</sub> intake may modify this association (21, 22).

**Neural tube defects**

Neural tube defects (NTD) may result in anencephaly or spina bifida, devastating and sometimes fatal birth defects. The defects occur between the 21st and 27th days after conception, a time when many women do not realize they are pregnant (23). Randomized controlled trials have demonstrated 60% to 100% reductions in
NTD cases when women consumed folic acid supplements in addition to a varied diet during the month before and the month after conception. Increasing evidence indicates that the homocysteine-lowering effect of folic acid plays a critical role in lowering the risk of NTD (24). Homocysteine may accumulate in the blood when there is inadequate folate and/or vitamin B₁₂ for effective functioning of the methionine synthase enzyme. Decreased vitamin B₁₂ levels in the blood and amniotic fluid of pregnant women have been associated with an increased risk of NTD, suggesting that adequate vitamin B₁₂ intake in addition to folic acid may be beneficial in the prevention of NTD.

Alzheimer's disease and dementia

Individuals with Alzheimer's disease often have low blood levels of vitamin B₁₂. One study found lower vitamin B₁₂ levels in the cerebrospinal fluid of patients with Alzheimer's disease than in patients with other types of dementia, though blood levels of vitamin B₁₂ did not differ (25). The reason for the association of low vitamin B₁₂ status with Alzheimer's disease is not clear. Vitamin B₁₂ deficiency, like folate deficiency, may lead to decreased synthesis of methionine and S-adenosylmethionine, thereby adversely affecting methylation reactions. Methylation reactions are essential for the metabolism of components of the myelin sheath of nerve cells as well as neurotransmitters. Also, moderately increased homocysteine levels as well as decreased folate and vitamin B₁₂ levels have been associated with Alzheimer's disease and vascular dementia.

Some but not all studies have associated elevated homocysteine concentrations or decreased serum levels of vitamin B₁₂ with an increased risk of Alzheimer's disease. A case-control study of 164 patients with dementia of Alzheimer's type included 76 cases in which the diagnosis of Alzheimer's disease was confirmed by examination of brain cells after death (26). Compared to 108 control subjects without evidence of dementia, subjects with dementia of Alzheimer's type and confirmed Alzheimer's disease had higher blood homocysteine levels and lower blood levels of folate and vitamin B₁₂. Measures of general nutritional status indicated that the association of increased homocysteine levels and diminished vitamin B₁₂ status with Alzheimer's disease was not due to dementia-related malnutrition (26). In another study, low serum vitamin B₁₂ (< 150 pmol/L) or folate (< 10 nmol/L) levels were associated with a doubling of the risk of developing Alzheimer's disease in 370 elderly men and women followed over three years (27). In a sample of 1,092 men and women without dementia followed for an average of ten years, those with higher plasma homocysteine levels at baseline had a significantly higher risk of developing Alzheimer's disease and other types of dementia (28). Specifically, those with plasma homocysteine levels greater than 14 micromol/L had nearly double the risk of developing Alzheimer's disease. A study in 650 elderly men and women reported that the risk of elevated plasma homocysteine levels was significantly higher in those with lower cognitive function scores (29). A prospective study in 816 elderly men and women reported that those with elevated homocysteine levels (> 15 micromol/L) had a significantly higher risk of developing Alzheimer's disease or dementia, but vitamin B₁₂ status was not related to risk of Alzheimer's disease or dementia in this study (30). Similarly, another prospective study in 965 older adults found that vitamin B₁₂ status was not related to the risk of Alzheimer's disease (31). Further, a prospective study in 1,041 older adults, followed for a median of 3.9 years, found that vitamin B₁₂ dietary intake was not associated with risk of developing Alzheimer's disease (32).

B vitamin supplementation is commonly used to treat hyperhomocysteinemia. A recent randomized, double-blind, placebo-controlled clinical trial in 253 older individuals with plasma homocysteine concentrations equal to or greater than 13 micromol/L found that daily B vitamin supplementation (1 mg folic acid, 0.5 mg vitamin B₁₂, and 10 mg vitamin B₆) for two years did not affect measures of cognitive performance despite an average 4.36 micromol/L reduction in plasma homocysteine concentrations (33). Another randomized, double-blind, placebo-
controlled study in 195 elderly adults reported that oral vitamin B₁₂ supplementation (1 mg daily) for six months had no effect on measures of cognitive function (34). Several of the homocysteine-lowering trials primarily focused on assessing cardiovascular disease risk will also assess measures of cognitive function (35). Thus, the findings of these ongoing trials may provide insight into whether long-term B vitamin supplementation is protective against dementia.

**Depression**

Observational studies have found as many as 30% of patients hospitalized for depression are deficient in vitamin B₁₂ (36). A cross-sectional study of 700 community-living, physically disabled women over the age of 65 found that vitamin B₁₂ deficient women were twice as likely to be severely depressed as non-deficient women (37). A population-based study in 3,884 elderly men and women with depressive disorders found that those with vitamin B₁₂ deficiency were almost 70% more likely to experience depression than those with normal vitamin B₁₂ status (38). The reasons for the relationship between vitamin B₁₂ deficiency and depression are not clear but may involve S-adenosylmethionine (SAMe). Vitamin B₁₂ and folate are required for the synthesis of SAMe, a methyl group donor essential for the metabolism of neurotransmitters whose bioavailability has been related to depression. This hypothesis is supported by several studies that have shown supplementation with SAMe improves depressive symptoms (39-42). Because few studies have examined the relationship of vitamin B₁₂ status and the development of depression over time, it cannot yet be determined if vitamin B₁₂ deficiency plays a causal role in depression. However, due to the high prevalence of vitamin B₁₂ deficiency in older individuals, it may be beneficial to screen for vitamin B₁₂ deficiency as part of a medical evaluation for depression.

**Sources**

**Food sources**

Only bacteria can synthesize vitamin B₁₂. Vitamin B₁₂ is present in animal products such as meat, poultry, fish (including shellfish), and to a lesser extent milk, but it is not generally present in plant products or yeast (1). Fresh pasteurized milk contains 0.9 mcg per cup and is an important source of vitamin B₁₂ for some vegetarians (6). Those vegetarians who eat no animal products need supplemental vitamin B₁₂ to meet their requirements. Also, individuals over the age of 50 should obtain their vitamin B₁₂ in supplements or fortified foods like fortified cereal because of the increased likelihood of food-bound vitamin B₁₂ malabsorption.

Most people do not have a problem obtaining the RDA of 2.4 mcg/day of vitamin B₁₂ in food. In the United States, the average intake of vitamin B₁₂ is about 4.5 mcg/day for young adult men, and 3 mcg/day for young adult women. In a sample of adults over the age of 60, men were found to have an average dietary intake of 3.4 mcg/day and women had an average dietary intake of 2.6 mcg/day (6). Some foods with substantial amounts of vitamin B₁₂ are listed in the table below along with their vitamin B₁₂ content in micrograms (mcg).

For more information on the nutrient content of specific foods, search the USDA food composition database.

<table>
<thead>
<tr>
<th>Food</th>
<th>Serving</th>
<th>Vitamin B₁₂ (mcg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clams (steamed)</td>
<td>3 ounces</td>
<td>84.0</td>
</tr>
<tr>
<td>Mussels (steamed)</td>
<td>3 ounces</td>
<td>20.4</td>
</tr>
<tr>
<td>Food</td>
<td>Serving Size</td>
<td>Calories</td>
</tr>
<tr>
<td>------------------</td>
<td>--------------</td>
<td>----------</td>
</tr>
<tr>
<td>Crab (steamed)</td>
<td>3 ounces</td>
<td>8.8</td>
</tr>
<tr>
<td>Salmon (baked)</td>
<td>3 ounces*</td>
<td>2.4</td>
</tr>
<tr>
<td>Rockfish (baked)</td>
<td>3 ounces</td>
<td>1.0</td>
</tr>
<tr>
<td>Beef (cooked)</td>
<td>3 ounces</td>
<td>2.1</td>
</tr>
<tr>
<td>Chicken (roasted)</td>
<td>3 ounces</td>
<td>0.3</td>
</tr>
<tr>
<td>Turkey (roasted)</td>
<td>3 ounces</td>
<td>0.3</td>
</tr>
<tr>
<td>Egg (poached)</td>
<td>1 large</td>
<td>0.6</td>
</tr>
<tr>
<td>Milk (skim)</td>
<td>8 ounces</td>
<td>0.9</td>
</tr>
<tr>
<td>Brie (cheese)</td>
<td>1 ounce</td>
<td>0.5</td>
</tr>
</tbody>
</table>

*A three-ounce serving of meat or fish is about the size of a deck of cards.

**Supplements**

Cyanocobalamin is the principal form of vitamin B₁₂ used in supplements but methylcobalamin is also available as a supplement. Cyanocobalamin is available by prescription in an injectable form and as a nasal gel for the treatment of pernicious anemia. Over-the-counter preparations containing cyanocobalamin include multivitamin, vitamin B-complex, and vitamin B₁₂ supplements (43).

**Safety**

**Toxicity**

No toxic or adverse effects have been associated with large intakes of vitamin B₁₂ from food or supplements in healthy people. Doses as high as 1 mg (1000 mcg) daily by mouth or 1 mg monthly by intramuscular (IM) injection have been used to treat pernicious anemia without significant side effects. When high doses of vitamin B₁₂ are given orally, only a small percentage can be absorbed, which may explain the low toxicity. Because of the low toxicity of vitamin B₁₂, no tolerable upper intake level (UL) was set by the Food and Nutrition Board in 1998 when the RDA was revised (6).

**Drug interactions**

A number of drugs reduce the absorption of vitamin B₁₂. Proton pump inhibitors (e.g., omeprazole and lansoprazole), used for therapy of Zollinger-Ellison syndrome and gastroesophageal reflux disease (GERD), markedly decrease stomach acid secretion required for the release of vitamin B₁₂ from food but not from supplements. Long-term use of proton pump inhibitors has been found to decrease blood vitamin B₁₂ levels. However, vitamin B₁₂ deficiency does not generally develop until after at least three years of continuous therapy (44). Another class of gastric acid inhibitors known as H₂-receptor antagonists (e.g., Tagamet, Pepsid, Zantac), often used to treat peptic ulcer disease, has also been found to decrease the absorption of vitamin B₁₂ from food. Because inhibition of gastric acid secretion is not as prolonged as with proton pump inhibitors H₂-receptor antagonists have not been found to cause overt vitamin B₁₂ deficiency even after long-term use (45). Individuals taking drugs that inhibit gastric acid secretion should consider taking vitamin B₁₂ in the form of a supplement because gastric acid is not required for its absorption. Other drugs found to inhibit vitamin B₁₂ absorption from food include cholestyramine (a bile acid-binding resin used in the treatment of high...
cholesterol), chloramphenicol and neomycin (antibiotics), and colchicine (anti-gout medicine). Metformin, a medication for individuals with type 2 (non-insulin dependent) diabetes, decreases vitamin B₁₂ absorption by tying up free calcium required for absorption of the IF-B₁₂ complex. This effect is correctable by drinking milk or taking calcium carbonate tablets along with food or supplements (5). Previous reports that megadoses of vitamin C destroy vitamin B₁₂ have not been supported (46) and may have been an artifact of the assay used to measure vitamin B₁₂ levels (6).

Nitrous oxide, a commonly used anesthetic, inhibits both of the vitamin B₁₂- dependent enzymes and can produce many of the clinical features of vitamin B₁₂ deficiency, such as megaloblastic anemia or neuropathy. Because nitrous oxide is commonly used for surgery in the elderly, some experts feel vitamin B₁₂ deficiency should be ruled out prior to its use (4, 12).

Large doses of folic acid given to an individual with an undiagnosed vitamin B₁₂ deficiency could correct megaloblastic anemia without correcting the underlying vitamin B₁₂ deficiency, leaving the individual at risk of developing irreversible neurologic damage (6). For this reason the Food and Nutrition Board of the Institute of Medicine advises that all adults limit their intake of folic acid (supplements and fortification) to 1000 mcg (1 mg) daily.

**Linus Pauling Institute Recommendation**

A varied diet should provide enough vitamin B₁₂ to prevent deficiency in most individuals 50 years of age and younger. Individuals over the age of 50, strict vegetarians, and women planning to become pregnant should take a multivitamin supplement daily or eat a fortified breakfast cereal, which would ensure a daily intake of 6 to 30 mcg of vitamin B₁₂ in a form that is easily absorbed. Higher doses of vitamin B₁₂ supplements are recommended for patients taking medications that interfere with its absorption (see Drug interactions).

**Older adults (> 50 years)**

Because vitamin B₁₂ malabsorption and vitamin B₁₂ deficiency are more common in older adults, some respected nutritionists recommend that adults older than 50 years take 100 to 400 mcg/day of supplemental vitamin B₁₂, an amount provided by a number of vitamin B-complex supplements.

**References**

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