

B Vitamins: Functions and Uses in Medicine

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Abstract

B vitamins are a group of 8 water-soluble vitamins. The body does not store them, so they need to be replaced daily. B vitamins are found in animal proteins, dairy products, leafy green vegetables, and beans. Overall, their function can generally be divided into catabolic metabolism, leading to energy production, and anabolic metabolism, resulting in bioactive molecules. They are critical cofactors for axonal transport, synthesis of neurotransmitters, and many cellular metabolic pathways. B vitamins are cofactors for many essential enzymes involved in the biosynthesis of RNA and DNA. B vitamin deficiencies have been considered as etiological factors in the development of various neurologic disorders and a broad spectrum of pathological states. Reductions in food intake and absorption efficiency in some populations, including the geriatric population, may warrant attention to their dietary B vitamin levels. Most B vitamins are generally safe even at intake levels reached with fortified food or supplements.

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B Vitamins: Functions and Uses in Medicine

B vitamins, also known as B-complex vitamins, play essential roles in catabolic and anabolic metabolism. These 8 water-soluble vitamins are excreted in urine and require repletion daily. The B vitamins are identified as follows: thiamine (B₁), riboflavin (B₂), niacin (B₃), pantothenic acid (B₅), pyridoxine (B₆), biotin (B₇), folate (B₉), and cobalamin (B₁₂). B vitamins act as coenzymes in several enzymatic processes that support every aspect of cellular physiological functioning, including major functions within the brain and nervous system. Any B vitamin deficiency

can negatively affect mitochondrial metabolism of amino acids, glucose, and fatty acids through the citric acid cycle and electron transport chain.¹

This article focuses on reviewing the members of the B complex, recommended daily intake (Table 1), biochemical functions, associated disease states (Table 2), drug interaction (Table 3), clinical uses (Table 4), and laboratory evaluation.

Vitamin B₁ (Thiamine)

FOOD SOURCES

Thiamine is found in most foods, though whole grains, pork, fish, and yeast are particularly rich sources. Processed foods such as

Vitamin	Men	Nonpregnant women	Pregnant women
B ₁	1.2 mg	1.1 mg	1.4 mg
B ₂	1.3 mg	1.1 mg	1.4 mg
B ₃	16 mg	14 mg	18 mg
B ₅	5 mg	5 mg	6 mg
B ₆	1-1.7 mg	1-1.7 mg	1.9 mg
B ₇	30 mcg	30 mcg	30 mcg
B ₉	400 mcg	400 mcg	600 mcg
B ₁₂	2.4 mcg	2.4 mcg	2.6 mcg

Table 1: Recommended daily intake for adults²

cereals, bread, dairy products, and infant formulas are fortified with thiamine because it is partially removed during processing.^{15,32}

BIOCHEMICAL FUNCTION

Thiamine is absorbed in the duodenum and converted with magnesium as a cofactor to its active form, thiamine pyrophosphate (TPP).³ TPP acts as a cofactor at crucial steps of the citric acid cycle and pentose phosphate pathway. TPP also plays a major role in the aerobic metabolism of glucose for energy production.^{3,33}

Low thiamine levels can cause altered mitochondrial activity, impaired oxidative metabolism, and reduced energy production. Cell death can occur, especially neurons, which are more vulnerable due to their high energy demand. Thiamine may perform as a free radical scavenger.^{3,33}

TPP is essential to the production of acetylcholine and myelin and the maintenance of glutamate, aspartate, and gamma-aminobutyric acid levels.^{3,33} Neuronal excitation and delirium can happen in thiamine deficiency because of low acetylcholine levels, decreased gamma-aminobutyric acid levels, and an increase in its precursor glutamate.^{3,33}

RISK FACTORS/DRUG INTERACTION

Chronic alcoholism can decrease thiamine intake and impair absorption and storage. Alcohol also inhibits thiamine phosphorylation which is essential for cellular function (Table 3).³

LABORATORY TESTING

Although thiamine can be measured in the serum or urine, doing so does not reflect storage levels.³³ The erythrocyte transketolase activity assay, including TPP, is the most reliable measure of thiamine functional status.²⁵

THIAMINE DEFICIENCY/TOXICITY

Common symptoms of thiamine deficiency are seen mostly with alcoholism and comprise 2 syndromes: Wernicke-Korsakoff syndrome and beriberi.³³

Wernicke-Korsakoff syndrome can present with 2 disorders. 1) Wernicke encephalopathy appears at the beginning of the disease course, presenting with a triad of ataxia, ophthalmoplegia, and altered mental status. Head imaging may show noninflammatory brain lesions, petechial hemorrhaging, and demyelination.^{15,33,34} 2) Korsakoff psychosis may develop if left untreated, consisting of delirium and permanent memory loss. Wernicke-Korsakoff syndrome should be treated emergently to prevent disease progression and permanent brain damage.^{33,34}

Beriberi's early symptoms include nausea, suppressed appetite, constipation, fatigue, mental suppression, peripheral neuropathy, and weight loss. Symptoms can manifest as either wet beriberi or dry beriberi as the disease progresses. Wet beriberi presents with cardiomyopathy, heart failure, edema, warm extremities, pleural effusions, and pulmonary edema. Dry beriberi affects mainly the peripheral nervous system, causing paresthesia, foot drop, muscle wasting, numbness, and absent ankle reflexes (Table 2).³³

TREATMENT/CLINICAL USES

Due to the potentially devastating manifestations of thiamine deficiency, especially Wernicke encephalopathy, emergent parenteral repletion is recommended to ensure adequate absorption. Thiamine should be started before any carbohydrate administration. The Royal College of Physicians recommends thiamine 500 mg intravenously (IV) 3 times daily for 3 days to be followed with 250 mg IV or intramuscularly (IM) once daily for 5 days or until clinical improvement stops. Prophylactic IV or IM thiamine should be given to all cases of severe alcohol withdrawal, poor diet, and malnutrition at a dose of 100 mg once daily for 3-5 days (Table 4).^{3,15,34}

Vitamin B₂ (Riboflavin)

FOOD SOURCES

Riboflavin is found naturally in eggs, dairy products, green vegetables, meat, mushrooms, and almonds. It is also available as a supplement and added to rice, corn, and flour, making deficiency in the United States uncommon.²⁴

Vitamin	Bioactive coenzyme	Deficiency symptoms	Neurologic symptoms of deficiency	Risk factor(s) for deficiency
Thiamine (B ₁)	TPP	Mild: fatigue, anorexia, and impaired reaction to stress Deficiency: Beriberi, endocarditis, arrhythmia, and sudden death ¹	Mild: irritability, sleep disturbance, peripheral neuropathy, and confusion Deficiency: Wernicke-Korsakoff syndrome ¹	<ul style="list-style-type: none"> - Poor intake: chronic alcoholism, carbohydrate loading, IV/PO without adequate thiamine intake, and malnutrition (eg, HIV, chemotherapy) - Impaired absorption: gastrointestinal surgical procedures, including bariatric surgical procedures - Increased utilization: pregnancy, lactation, hyperthyroidism, and refeeding syndrome - Increased loss: diarrhea, diuretics, advanced kidney disease, or dialysis^{1,3}
Riboflavin (B ₂)	Flavoproteins: flavin adenine dinucleotide or flavin mononucleotide (redox reactions)	Stomatitis, cheilitis, glossitis, dermatitis, eye irritation, cataracts, and anemia ¹⁴	Fatigue, migraine, and personality changes ¹⁴	<ul style="list-style-type: none"> - Anorexia nervosa - Malabsorptive syndromes - Prolonged use of barbiturates - Uncommon inborn errors of metabolism - Pregnancy - Dialysis or diarrhea⁵
Niacin (B ₃)	Nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate	Pellagra: dermatitis, photodermatitis, burning and twitching in extremities, and diarrhea ¹	Depression, anxiety, memory loss, and psychotic symptoms ¹	<ul style="list-style-type: none"> - Low tryptophan intake - High corn diet - Carcinoid syndrome - Prolonged use of isoniazid - Hartnup disease^{6,7}
Pantothenic acid (B ₅)	Coenzyme A ¹	Diarrhea, numbness, burning sensations, and dermatitis ¹⁵	Encephalopathy, demyelination, insomnia, and behavioral changes ¹²	<ul style="list-style-type: none"> - Deficiency is rare unless associated with another vitamin B deficiency¹⁸
Pyridoxine, pyridoxal, pyridoxamine (B ₆)	Pyridoxal 5'-phosphate	Anemia ⁹	Cognitive impairment, irritability, depression, peripheral neuropathy, and convulsion ^{19,10}	<ul style="list-style-type: none"> - Alcoholism, renal insufficiency, rheumatoid arthritis, and malabsorption syndromes⁹
Biotin (B ₇)	Biotin	Dermatitis and tingling in extremities ¹¹	Depression, lethargy, and seizures ¹¹	<ul style="list-style-type: none"> - Biotinidase deficiency, alcoholism, epileptic medications, pregnancy, or breastfeeding¹²
Folic acid, folate (B ₉)	Methyltetrahydrofolate	Megaloblastic anemia, peripheral neuropathy, and spinal cord lesion ¹	Behavioral changes, affective disorders, psychosis, and dementia ¹	<ul style="list-style-type: none"> - Genetic polymorphism <i>MTHFR</i> C667T - Malabsorption - Poor intake - Hemodialysis - Hemolysis²
Cobalamins (B ₁₂)	Methylcobalamin and 5'-deoxyadenosylcobalamin ¹	Same as folic acid deficiency ^{13,14}	Same as folic acid deficiency ^{13,14}	<ul style="list-style-type: none"> - Pernicious anemia - Malabsorption (eg, gastric bypass, celiac disease, and Crohn's disease) - Vegan or poor oral intake^{13,14}

Table 2: B vitamins, coenzymes, deficiency symptoms, and risk factors for deficiency

HIV = Human immunodeficiency virus; IV/PO = intravenous-to-oral; TPP = thiamine pyrophosphate.

BIOCHEMICAL FUNCTION

Riboflavin active forms are essential in synthesizing niacin, folic acid, vitamin B₆, and all heme proteins. It is also needed for carbohydrate, protein, and fat metabolism into glucose. Its antioxidant effect is vital to cellular respiration and function in the immune system.^{1,4}

RISK FACTORS/DRUG INTERACTION

Anticonvulsants, anticholinergics, and phenothiazine decrease the absorption of riboflavin (Table 3).^{5,35} Deficiency can be seen in liver disease, alcoholism, and hemodialysis.^{5,35}

LABORATORY TESTING

The erythrocyte glutathione reductase activity coefficient is the most sensitive test used to measure vitamin B₂ levels. The fluorometric

measurement of 24-hour urinary excretion with a rate of less than 40 mcg/d indicates a deficiency.¹⁶

RIBOFLAVIN DEFICIENCY/TOXICITY

Riboflavin toxicity is rare due to its efficient excretion by the kidneys.^{4,24} Deficiency, however, can lead to skin abnormalities, angular stomatitis, cheilosis, depression, fatigue, anemia, sore throat, hair loss, liver toxicity, and nervous system issues (Table 2).^{4,24}

TREATMENT/CLINICAL USES

Riboflavin deficiency and its symptomatology are mostly reversible through diet and supplementation.^{4,24} Riboflavin may be used to prevent cataracts and lower homocysteine levels. Riboflavin is rated as level B evidence for migraine headache prophylaxis by the American Academy of Neurology (Table 4).²⁴

Vitamin	Risk factors for deficiency	Mechanism
Thiamine (B ₁)	<ul style="list-style-type: none"> - Diuretics¹⁵ - Fluorouracil (5-fluorouracil)¹⁵ - High carb diet³ 	<ul style="list-style-type: none"> - Increases urinary loss¹⁵ - Increases thiamine metabolism - Aerobic glucose breakdown consumes thiamine³
Riboflavin (B ₂)	<ul style="list-style-type: none"> - Long-term barbiturate use^{5,16} - Tricyclic antidepressant and contraceptive pills¹⁶ - Tetracyclines¹⁶ 	<ul style="list-style-type: none"> - Impairs riboflavin function⁵ - Decreases riboflavin absorption¹⁶ - Riboflavin decreases tetracycline absorption¹⁶
Niacin (B ₃)	<ul style="list-style-type: none"> - Alcohol¹ - Nicotine patches - Azathioprine, 6-mercaptopurine, or 5-fluorouracil⁶ - Isoniazid^{2,6,7} 	<ul style="list-style-type: none"> - Decreases niacin absorption¹ - Worsens flushing. - Decreases tryptophan conversion to niacin^{6,7} - Decreases tryptophan production^{2,6,7}
Pantothenic acid (B ₅)	<ul style="list-style-type: none"> - Antibiotics (especially tetracyclines), cholinesterase inhibitors, and memantine^{8,17} 	<ul style="list-style-type: none"> - Vitamin B₅ interferes with the absorption and effectiveness of these drugs¹⁷
Pyridoxine, pyridoxal, pyridoxamine (B ₆)	<ul style="list-style-type: none"> - Cycloserine (tuberculosis treatment) - Antiepileptic drugs (valproic acid, carbamazepine, and phenytoin)^{9,18} - INH^{9,19,20} 	<ul style="list-style-type: none"> - Increases urine excretion of B₆^{9,18} - Increases the catabolism of B₆^{9,18} - Inhibits the action of B₆^{9,18}
Biotin (B ₇)	<ul style="list-style-type: none"> - Anticonvulsants¹² - Troponin - Thyroid function tests - 25-hydroxy vitamin D²⁹ 	<ul style="list-style-type: none"> - Increases biotin metabolism² - False low results - False hyperthyroid results - False positive or abnormal results²¹
Folic acid, folate (B ₉)	<ul style="list-style-type: none"> - Antiepileptic drugs, including gabapentin - Methotrexate - Adrucil, Hydrea, Daraprim, Bactrim, and Septra - Metformin and cholestyramine^{2,22,23} 	<ul style="list-style-type: none"> - Impairs absorption and increases metabolism - Causes functional deficiency - Affects folate metabolism - Decreases absorption^{2,22,23}
Cobalamin (B ₁₂)	<ul style="list-style-type: none"> - Metformin, antacid, aminoglycoside antibiotics, and colchicine¹⁴ 	<ul style="list-style-type: none"> - Decreases B₁₂ absorption¹⁴

Table 3: B vitamins and possible risk factors and drug interaction

INH = brand name of isoniazid; Adrucil = brand name of 5-fluorouracil; Hydrea = brand name of hydroxyurea; Daraprim = brand name of pyrimethamine; Bactrim = brand name of trimethoprim/sulfamethoxazole; and Septra = brand name of trimethoprim/sulfamethoxazole.

Vitamin B₃ (Niacin)

FOOD SOURCES

Niacin is found in animal and plant-based foods, including soy, nuts, seeds, legumes, and grains. Many grains, such as bread and cereals, and infant formulas are fortified with niacin.²

BIOCHEMICAL FUNCTION

Niacin is metabolized from tryptophan and works as a precursor for nicotinamide adenine dinucleotide and nicotinamide adenine dinucleotide phosphate coenzymes. Both are needed for DNA repair and cholesterol synthesis.^{2,32}

RISK FACTORS/DRUG INTERACTION

Low iron, riboflavin, or vitamin B₆ levels decrease the conversion of tryptophan to niacin (Table 3).^{2,32}

LABORATORY TESTING

Testing is not widely available, but riboflavin can be assessed by measuring the urinary N-methylnicotinamide or erythrocyte nicotinamide adenine dinucleotide to nicotinamide adenine dinucleotide phosphate ratio.^{2,35}

NIACIN DEFICIENCY/TOXICITY

Pellagra, caused by niacin deficiency, is rare in developed countries because their diets have the average recommended amount of niacin. Pellagra is characterized by “the 3 Ds”: dementia, diarrhea, and dermatitis. Other associated manifestations include memory loss, depression, disorientation, headaches, apathy, fatigue, vomit, a swollen mouth, and a scaly rash on sun-exposed skin. Pellagra may be lethal if not treated.^{2,6,7,32}

Toxicity may occur with doses above 3 g/d, leading to flushing, macular edema, macular cysts, hyperglycemia, hyperuricemia, and liver toxicity in severe cases.² The upper limit of dietary intake should not exceed 35 mg/d (Table 2).¹

TREATMENT/CLINICAL USES

The nicotinamide form of niacin is preferred to treat deficiency because it does not cause flushing, itching, or burning sensations.^{6,7} Nicotinamide is recommended to treat acute pellagra with a dose of 100 mg every 6 hours orally until resolution of substantial acute symptoms, followed by 50 mg orally every 8-12 hours until all skin lesions are

Vitamin	Clinical uses	Suggested regimen
Thiamine (B ₁)	- Wernicke-Korsakoff syndrome treatment	- The European Federation of Neurological Societies: Thiamine 200 mg IV 3 times daily until improvement stops ^{3,24} - The Royal College of Physicians: Thiamine 500 mg IV 3 times daily for 3 d to be followed with 250 mg IV or IM once daily for 5 d or until clinical improvement stops - Thiamine should be given before any carbohydrates ^{15,25}
	- Alcoholism/Clinical Institute Withdrawal Assessment for Alcohol (CIWA) protocol ¹⁵	- Thiamine 100 mg IV once daily for 3-5 d ²
	- Bariatric surgery ¹⁵	- Thiamine 100 mg IV for 7-14 d in mild deficiency - Thiamine 500 mg/d IV for 3-5 d followed by 250 mg/d for 3-5 d or until symptoms resolve followed by 100 mg/d orally indefinitely in severe deficiency ¹⁵
Riboflavin (B ₂)	- To treat stomatitis, cheilitis, and glossitis ²⁴ - Cataract prevention ⁴ - Migraine prophylaxis ²⁴	- 0.5 mg/kg orally daily until symptoms resolve - 400 mg daily for 5-6 y ⁴ - 400 mg daily for a minimum of 3 mo (evidence level B) ²⁴
Niacin (B ₃)	- To treat pellagra ^{6,7}	- Nicotinamide 100 mg every 6 h orally until resolution of acute major symptoms ^{6,7}
Pantothenic acid (B ₅)	- Acne, anxiety, allergies, rheumatoid arthritis ^{8,26} - Accelerate wound healing, lowers triglyceride levels ^{8,17,26} (Small studies)	- 5 mg orally daily ^{2,8}
Pyridoxine, pyridoxal, pyridoxamine (B ₆)	- INH overdose-related seizure or toxic INH dose without seizure ^{19,20}	- Pyridoxine dose should be equivalent to the maximum suspected amount of ingested isoniazid. If ingested isoniazid is unknown, 5 g of pyridoxine should be given IV at a rate of 0.5-1 g/min pending seizures to discontinue or maximum dose given ^{19,20}
	- Ethylene glycol overdose ²⁰	- 50-100 mg IV every 6 h ²⁰
	- Nausea and vomiting of pregnancy ²⁷	- 10-25 mg orally every 8 h (evidence rating A) ²⁷
	- Premenstrual syndrome ²⁸	- 50-100 mg daily (limited evidence) ²⁸
Biotin (B ₇)	- Inherited enzyme deficiency ¹² - Brittle hair syndrome ¹²	- 10,000-30,000 μg/d orally ²⁹ - 300-3000 μg/d (low-quality evidence) ¹²
Folic acid, folate (B ₉)	- Megaloblastic anemia ³⁰ - Pregnancy - Dialysis and malabsorption - Hemolysis ³⁰ - High risk for neural tube defects ³⁰	- 1-5 mg orally once daily for 4 mo or until term in pregnancy ³⁰ - 0.4-0.8 mg/d (Grade A) - 5 mg orally once daily ³⁰ - 1 mg orally daily - 4 mg orally daily ³⁰
Cobalamin (B ₁₂)	- B ₁₂ deficiency maintenance dose - Megaloblastic anemia/B ₁₂ deficiency without neurologic symptoms ^{14,30} - In symptomatic anemia, neurologic symptoms, or pregnancy ^{14,29,30} - Bariatric surgery ³¹ - Concurrent folate and B ₁₂ deficiency ³¹	- 1000 mcg IM monthly or 1000-2000 mcg orally daily until deficiency is corrected ^{14,30} - 1000 mcg IM 3 times weekly for 2 wk ^{14,29-31} - 1000 mcg IM every other day for 3 wk followed by 1000 mcg orally once monthly ^{14,29,30} - 1000 mcg orally daily indefinitely ³¹ - B ₁₂ should be replaced first ³¹

Table 4: B vitamins and possible clinical uses

IM = Intramuscularly; INH = brand name of isoniazid.; IV = intravenously.

healed.^{6,7} Pellagra patients should avoid sun exposure and alcohol intake.⁶ Although niacin lowers low-density lipoprotein and triglycerides and increases high-density lipoprotein, current evidence has shown no decreased mortality or cardiovascular events (Table 4).^{32,36}

Vitamin B₅ (Pantothenic Acid)

FOOD SOURCES

Small amounts of pantothenic acid are typically found in nearly all food, with more substantial quantities in fortified cereals, infant formulas, dried foods, mushrooms, eggs, fish, avocados, chicken, beef, pork, sunflower seeds, sweet potatoes, and lentils.²

BIOCHEMICAL FUNCTION

Pantothenic acid is essential in the biosynthesis of coenzyme A, cholesterol, fatty acids, and acetylcholine.^{8,26}

RISK FACTORS/DRUG INTERACTION

There is no known relevant clinical interaction with medications or nutrients (Table 3).²

LABORATORY TESTING

Pantothenic acid, also known as P-5-P, can be measured via radioimmunoassay or 24-hour urinary excretion. Levels of pantothenic acid excretion below 1 mg/d usually indicate deficiency.^{2,35} Serum pantothenate concentration does not correlate with its status, but a level of less than 50 mcg/mL can aid the diagnosis of deficiency.⁸

PANTOTHENIC DEFICIENCY/TOXICITY

Although rare in developed countries, deficiency symptoms may include increased arthritic pain, fatigue, irritability, headaches, and gastrointestinal issues. Nearly all symptoms resolve after resuming intake of pantothenic acid (Table 2).^{2,8,26}

There is no report of pantothenic acid toxicity with high intakes.^{2,35}

TREATMENT/CLINICAL USES

There is weak evidence to support the clinical use of pantothenic acid in certain conditions like accelerating wound healing, lowering triglyceride levels, improving rheumatoid arthritis symptoms (Table 4).^{8,17,26}

Vitamin B₆ (Pyridoxine)

FOOD SOURCES

Pyridoxine is found in beef, poultry, starchy vegetables, noncitrus fruits, and fortified cereals.⁹

BIOCHEMICAL FUNCTION

Pyridoxal 5'-phosphate, the active form, is a coenzyme that supports numerous enzymes in performing various functions, including the maintenance of normal levels of homocysteine, supporting immune function and brain health, and the breakdown of carbohydrates, proteins, and fats.²

RISK FACTORS/DRUG INTERACTION

Several medications interfere with pyridoxine metabolism, including isoniazid and cycloserine (Seromycin), penicillamine, hydralazine, levodopa, and some anticonvulsants, which are antagonists to vitamin B₆ (Table 3).^{9,18}

LABORATORY TESTING

Pyridoxine function is best assessed by erythrocyte transaminase activity, with and without pyridoxal 5'-phosphate.^{18,35} Urinary pyridoxic acid excretion of more than 3.0 mmol/d is an indicator of adequate short-term pyridoxine status.¹⁸

PYRIDOXINE DEFICIENCY/TOXICITY

Pyridoxine deficiency is commonly associated with other B vitamin deficiencies, such as folic acid and vitamin B₁₂, and is rare in isolation.¹⁸

Deficiency of active pyridoxine is found in chronic alcohol dependence, chronic renal failure or autoimmune disorders, obesity, pregnancy, preeclampsia, eclampsia, and malabsorptive states such as celiac

disease, inflammatory bowel disease, and bariatric surgery.^{9,18}

Pyridoxine deficiency is associated with microcytic anemia, electroencephalographic abnormalities, dermatitis with cheilosis, glossitis, depression, confusion, and weakened immune function.^{9,18} Individuals with mild deficiency might show no symptoms or signs for months or years. Pyridoxine deficiency in infants causes irritability, abnormally acute hearing, and convulsive seizures (Table 2).⁹

Toxicity can lead to peripheral neuropathy; thus, the recommended upper limit is 100 mg/d.^{9,18}

TREATMENT/CLINICAL USES

Pyridoxine may have therapeutic uses in several areas. Because pyridoxine is essential in serotonin and dopamine synthesis, observational studies have shown some evidence that it can be a helpful adjunct in treating depression, aggressive behavior, and migraine headaches.¹⁰ Pyridoxine deficiency is also hypothesized to cause idiopathic carpal tunnel syndrome.³⁷ Pyridoxine (along with folic acid and B₁₂) have been shown to lower homocysteine levels, but there is no evidence that supplementation decreases the chance of heart disease, stroke, or Alzheimer's dementia.^{2,9} It may also lessen premenstrual syndrome, but more robust evidence is needed.²⁸ One common use of pyridoxine is in treating pregnancy-induced nausea and vomiting, as a monotherapy or in combination with doxylamine.²⁷ Pyridoxine is the emergency antidote for isoniazid (INH) overdose, hydralazine, ethylene glycol, and gyromitrin mushroom poisoning (Table 4).^{19,20}

Vitamin B₇ (Biotin)

FOOD SOURCES

Biotin is found naturally in organ meats, eggs, fish, seeds, soybeans, and nuts but is also available through supplementation.¹¹

BIOCHEMICAL FUNCTION

Biotin plays an essential role in gene regulation, cell signaling, and replication. It catalyzes the metabolism of fatty acids, glucose, and amino acids.¹¹

RISK FACTORS/DRUG INTERACTION

A large dose of biotin can interfere with clinical assays that use streptavidin-biotin technology, including troponins, thyroid function tests, and vitamin D tests.²¹ Anticonvulsant treatment with carbamazepine, primidone, phenytoin, and

phenobarbital has been associated with biotin deficiency (Table 3).^{11,12}

LABORATORY TESTING

Biotin deficiency is most accurately measured via urinary excretion of 3-hydroxyisovaleric acid. Serum biotin levels are not sensitive enough to reflect intake or sufficiency.^{2,11}

BIOTIN DEFICIENCY/TOXICITY

Biotin deficiency is rare outside of high-risk populations, such as those who experience biotinidase deficiency, alcoholism, chronic use of epileptic medications, and pregnant or breastfeeding women. Excessive biotin levels have no known toxic effects.^{2,12}

Biotin deficiency is associated with hair thinning, a scaly rash around the eyes, nose, mouth, and perineum, nail changes, skin infections, and neurologic symptoms such as ataxia, seizures, depression, lethargy, and paresthesia (Table 2).^{2,11}

TREATMENT/CLINICAL USES

Supplemental dosing for biotin deficiency has not been established. Evidence is insufficient to support the use of biotin for other reasons (Table 4).¹²

Vitamin B₉ (Folate)

FOOD SOURCES

Folate is present in plenty of foods, with the highest levels in dark green leafy vegetables, nuts, beans, dairy products, meat, poultry, grains, and brussels sprouts.^{2,22}

BIOCHEMICAL FUNCTION

Folate is crucial for nucleic acid synthesis and red blood cell production. It is involved in converting homocysteine to methionine, which is essential for hematopoiesis and prevention of megaloblastic anemia.^{2,22,38}

RISK FACTORS/DRUG INTERACTION

Antiepileptics and sulfasalazine can reduce the absorption of folate.^{2,22,23} Certain groups of people are more likely to have inadequate folate intake and deficiency, such as women of childbearing age and Black women. The recommended dietary intake is increased during pregnancy and lactation (Table 3).^{2,22} Other high-risk groups include those with the *MTHFR* gene mutations, which are relatively common. C677T polymorphism is the most common variant associated with a reduced ability to convert

folic acid into its active form, L-methylfolate. About 16% of White people and 25% of Hispanic people are homozygous for the *MTHFR* T677 allele. Supplementation with L-methylfolate (5-MTHF) should be considered for those with *MTHFR* variants.^{2,22}

LABORATORY TESTING

Serum folate levels are susceptible to recent dietary intake, making erythrocyte folate concentration helpful to confirm a long-term deficiency. Homocysteine levels will also rise with folate deficiency.^{2,22}

FOLATE DEFICIENCY/TOXICITY

Deficiency is associated with poor diet, alcoholism, and malabsorptive disorders.^{22,30}

Folate deficiency can lead to megaloblastic anemia, characterized by large erythrocytes with abnormal nuclei. Patients may report weakness, fatigue, poor concentration, irritability, headaches, and palpitations. Deficiency can also cause oral ulcerations and changes in skin, hair, and fingernails.^{22,23} Maternal low folate levels during pregnancy increase the chance of congenital birth defects, including fetal neural tube defects, and congenital heart defects, in addition to low birth weight, preterm labor, and delayed fetal growth.^{38,39}

Concurrent B₁₂ deficiency should be ruled out before repletion of folate to reverse the megaloblastic anemia. Repletion of folic acid will correct the macrocytic anemia but will not prevent the neuropathy related to cobalamin deficiency and its toxic neurologic effects because of elevated methylmalonic acid levels.^{2,13,22}

The US National Toxicology Program found insufficient evidence for adverse effects due to folic acid with an upper intake recommended at 1000 mcg/d (Table 2).²

TREATMENT/CLINICAL USES

Treatment for megaloblastic anemia due to folate deficiency ranges from 1 to 5 mg/d, though some sources recommend as high as 15 mg/d. Folate supplementation is recommended for individuals taking methotrexate, sulfasalazine, and antiepileptic drugs.^{2,22,30}

The dosage for women of childbearing age should be 0.4–0.8 mg/d, with an increased amount of 4 mg/d for those at high risk for neural tube defects (family history or previous pregnancy with a neural tube defect, Table 4).³⁰

Vitamin B₁₂ (Cobalamin, Cyanocobalamin, Methylcobalamin)

FOOD SOURCES

Cobalamin is found in animal products and fortified foods.¹⁴

BIOCHEMICAL FUNCTION

Gastric acid helps to release cobalamin from animal protein. Cobalamin eventually combines with an intrinsic factor to absorb in the distal ileum. Interruption of this process can hinder its absorption, leading to megaloblastic anemia and neurologic disorders.^{13,14}

Cobalamin is required for red blood cell production, neurologic function, and myelin synthesis. It serves as a cofactor in DNA and RNA synthesis as well as hormone, protein, and lipid synthesis and metabolism.^{2,13}

RISK FACTORS/DRUG INTERACTION

Patients using proton pump inhibitors, H₂ receptor antagonists, colchicine, and metformin are more likely to have cobalamin malabsorption (Table 3).^{13,14,23}

LABORATORY TESTING

Elevated methylmalonic acid and homocysteine levels provide evidence of cobalamin deficiency. Cobalamin can be measured via serum, though some studies suggest it may not accurately reflect intracellular concentrations. Serum homocysteine levels will rise in cobalamin deficiency.^{2,13,14}

COBALAMIN, CYANOCOBALAMIN, AND METHYL-COBALAMIN DEFICIENCY/TOXICITY

Deficiency may present as megaloblastic anemia, fatigue, low appetite, and neuropsychiatric symptoms. If not treated, neuropsychiatric illness and irreversible neurologic damage occur.¹⁴ A more common presentation is low or marginal cobalamin levels of 200–300 pg/mL (148–221 pmol/L) without symptoms.^{13,14}

The most affected groups are older adults, patients with pernicious anemia, pregnant and lactating women, and those with gastrointestinal disorders.^{13,30} Individuals on a vegan diet should consider supplementation in addition to the geriatric population. High doses of cobalamin are unlikely to cause toxicity (Table 2).^{13,30}

TREATMENT/CLINICAL USES

The etiology of cobalamin deficiency needs to be considered before repletion. Patients with a vegan diet will have adequate vitamin B₁₂ absorption with oral supplementation. In contrast, those with intrinsic factor deficiency due to pernicious anemia or gastric bypass surgery will require parenteral supplementation. Once identified, cobalamin deficiency should be treated with IM injections of 1000 mcg 3 times weekly for 2 weeks followed by weekly injections for 1 month to replenish stores. Patients can then receive monthly cobalamin 1000 mcg injections or oral cobalamin 1000–2000 mcg daily for maintenance (Table 4).^{14,29,30}

Conclusion

B vitamins play a role in many critical reactions in human metabolism. Because they are water-soluble, they are not stored in the body and must be replaced daily. They are found naturally in various foods, supplements, and fortified processed foods. Reductions in food intake and absorption efficiency in some populations, including the older adult population, may warrant attention to their dietary B vitamin levels. However, additional research and clinical communication are needed regarding suboptimal levels of vitamin B in addition to outright deficiency. Fortunately, when deficiency does occur, the symptoms associated with it are often reversed with appropriate repletion.¹

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