The B Vitamins

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Faculty

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Faculty Disclosure

Contributing faculty, Evangeline Y. Samples, MS, RDN, LD, EdD, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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The division planner and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience

This course is designed for nurses and allied health professionals in all practice settings.

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Course Objective

The purpose of this course is to provide nurses with information about the importance of B vitamins for human health, so they can identify patients at risk of deficiency and provide nutrition counseling and education about recommended intake.

Learning Objectives

Upon completion of this course, you should be able to:

1. Outline the action, recommended intake, and effects of deficiency of the B vitamin thiamine.
2. Review the sources and potential effects of deficiency of riboflavin and niacin.
3. Describe the action, dietary sources, and potential deficiency issues associated with the other B vitamins.

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

The B vitamins are necessary for numerous metabolic processes. For example, they function as coenzymes in the metabolism of carbohydrates. Because the B vitamins are water-soluble, they are excreted in the urine and are not stored long term in body tissues. Therefore, they need to be replenished frequently through dietary intake and/or supplementation. This course explores the roles of thiamine, niacin, riboflavin, vitamin B6, vitamin B12, and folate in human nutrition, including the functions, daily requirements, food sources, deficiency, and toxicity of these vitamins.

THIAMINE

Thiamine, also called vitamin B1, functions as a coenzyme in the metabolism of carbohydrates and is essential in the metabolism of glucose [1; 2]. Thiamine is a cofactor for a number of enzymes, mostly those located within the mitochondria of cells. This vitamin plays vital roles in energy metabolism and the production of nucleic acids [2].

ABSORPTION OF THIAMINE

Thiamine is absorbed in the jejunum by active transport. Only a small percentage of ingested thiamine is absorbed, and excess thiamine is excreted in the urine [1]. The body does not store more than 30 mg of thiamine, and the half-life of thiamine is 9 to 18 days. For these reasons, thiamine must be replenished frequently through the diet [2].

DIETARY THIAMINE

Requirements are determined by sex and life stage. Boys and men 14 years of age and older require 1.2 mg thiamine per day, while girls and women 14 years of age and older require 1.1 mg per day. Individuals receiving hemodialysis or peritoneal dialysis have increased needs (1.5–2 mg) [1].

The richest sources of naturally occurring thiamine are meat (especially pork), whole grains, yeast, and legumes. Fortified foods are also a good source. To prevent widespread deficiencies, it is recommended that the target population should consume a fortified food daily. This is generally easily achieved, as food staples such as rice or wheat flour are often fortified with thiamine. Mandatory fortification levels range from 1.5–11 mg per kg of wheat flour [3]. There is no known tolerable upper intake level and no known toxicity for thiamine; however, using the lowest effective dose is recommended [1; 3].

EXCESS THIAMINE

There are limited data on excess thiamine consumption, and there is no established upper limit for thiamine consumption [1].

THIAMINE DEFICIENCY

Thiamine deficiency has numerous causes. It may be caused by inadequate intake, malabsorption, food-nutrient interactions, and increased excretion resulting from physically demanding occupations or spend large amounts of time training for active sports [1]. Other factors include aging, economic status, eating disorders, gastrointestinal conditions, parenteral nutrition, bariatric surgery, diabetes, and alcohol abuse. Pregnancy, lactation, and increased physical activity increase the need for thiamine [2].

Foods that Compromise Thiamine Status

Some food processing methods and food components compromise thiamine status in individuals. Industrial food processing depletes the thiamine content of food. Increased consumption of processed foods that contain simple carbohydrates without being supplemented with high levels of thiamine can lead to a phenomenon known as "high-calorie malnutrition."

As noted, foods that contain tannins can inactivate thiamine in the body, thereby putting an individual at risk for deficiency [2[. Tannins are found in tea, coffee, legumes (e.g., chickpeas, pinto beans), and berries (e.g., strawberries, raspberries) [1; 4]. Foods high in caffeine, theobromine, and theophylline,

including coffee, tea and chocolate, can also inactivate thiamine in the body [2]. Thiamine status may also be compromised by betel nuts, ferns, African silkworm larvae, and thiaminase-containing fish [3].

Thiamine Deficiency Caused by Genetic Disorders

Thiamine deficiency may be caused by genetic disorders or genetic factors. Four known genetic disorders can cause impairment of thiamine metabolism and transport. Carriers of loss-of-function mutations in *SLC19A2* develop a rare condition called thiamine-responsive megaloblastic anemia (TRMA), or Rogers syndrome [5]. The condition is an autosomal recessive disorder characterized by megaloblastic anemia, macrocytosis, diabetes mellitus, and sensorineural deafness. Other features of this disorder include optic atrophy, congenital heart defects, short stature, and epilepsy and stroke during infancy. Symptoms improve after administering high doses of thiamine [2].

Thiamine deficiency can also result from genetic factors with pathogenic gene mutations in key regulators of the thiamine pathway. These key regulators include thiamine pyrophosphokinase 1 (*TPK1*); thiamine diphosphate kinase (*TDPK*); thiamine triphosphate (*THTPA*); and the thiamine transporters *SLC25A19*, *SLC19A2/THTR1*, and *SLC19A3/THTR2* [2].

Systemic Effects of Thiamine Deficiency

Thiamine deficiency affects numerous body systems. The brain relies heavily on mitochondrial adenosine triphosphate (ATP) production and is vulnerable to thiamine deficiency. Cased of thiamine deficiency can result in mild neurological and psychiatric symptoms, such as confusion, sleep disturbances, and decreased memory. Anorexia, weight loss, muscle weakness, and cardiovascular effects (e.g., enlarged heart), are also potential symptoms of thiamine deficiency [1]. Encephalopathy and ataxia can occur in more severe cases. Prolonged thiamine deficiency may also lead to congestive heart failure, muscle atrophy, and death [2].

EVIDENCE-BASED PRACTICE RECOMMENDATION

According to the European Federation of Neurological Societies, thiamine is indicated for the treatment of suspected or manifest Wernicke encephalopathy. It should be given, before any carbohydrate, 200 mg thrice daily, preferably intravenously.

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Level of Evidence: Expert Opinion/Consensus Statement

The clinical syndrome of thiamine deficiency is referred to as beriberi. There are two forms of beriberi, each with a specific clinical presentation. Dry beriberi presents with neurological difficulties and can lead to peripheral neuropathy. Wet beriberi is a primarily cardiac presentation that leads to heart failure [3].

RIBOFLAVIN

Also called vitamin B2, riboflavin is involved in oxidation-reduction reactions [1]. In particular, it functions as flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) and participates in electron transport and the metabolism of lipids and drugs [6].

ABSORPTION OF RIBOFLAVIN

Most riboflavin is absorbed in the small intestine by carrier-mediated processes [7; 8]. However, the duodenum, stomach, and colon can also absorb this vitamin [7].

About 95% of riboflavin is food is bioavailable, and up to a maximum of roughly 27 mg may be absorbed in a single dose [1]. When the body has a deficiency of riboflavin, additional amounts of the vitamin will be absorbed to resolve the deficiency [8].

DIETARY RIBOFLAVIN

Major food sources for riboflavin include organ meats, poultry, fish, eggs, and dairy products such as milk and cheese. Grain products and fortified cereals are additional sources [1]. Certain vegetables such as spinach and beans can also provide riboflavin [7].

Natural grain products are low in riboflavin, but riboflavin bioavailability is enhanced when food is fortified [6]. Riboflavin is typically added to most vitamin-enriched products, such as cereals and baby foods. Moreover, some bacteria in the human microbiome can produce riboflavin [7].

EXCESS RIBOFLAVIN

No adverse effects of excess riboflavin consumption have been observed [1]. Excess riboflavin is excreted by the kidney [6].

RIBOFLAVIN DEFICIENCY

Riboflavin deficiency seldom occurs in isolation. When it does develop, it is typically in conjunction with other vitamin deficiencies, especially niacin and vitamin B6 [1]. Clinical symptoms of riboflavin deficiency occur after months of poor intake.

Certain populations are vulnerable to riboflavin deficiency. Up to 48% of vegans consume less than the recommended dietary reference intake (DRI) and are at risk of riboflavin deficiency. Athletes and others who engage in intense physical activity are at risk of deficiency due to the metabolic stress that occurs during sessions of increased physical activity [7].

Riboflavin deficiency can affect numerous body systems and functions, including iron utilization, the metabolism of tryptophan, mitochondrial function, and neurological and gastrointestinal tract functions [8]. Deficiency also impacts the metabolism of lipids and energy metabolism, the balance of oxidants and antioxidants (redox balance), and metabolism of drugs [6]. Signs and symptoms include sore throat, edema and hyperemia of the pharyngeal and oral mucous membranes, cheilosis, angular stomatitis, glossitis (magenta tongue), seborrheic dermatitis (dandruff), and normocytic anemia [1].

Riboflavin deficiency may be associated with the development of cataracts due to the impaired regeneration of reduced glutathione in the lens. Glutathione exists in high concentrations in the reduced form and protects the lens from oxidative damage [8].

Riboflavin Deficiency Caused by Genetic Disorders

Riboflavin deficiency may be caused by genetic disorders. Persistent riboflavin deficiency is seen in patients with Brown-Vialetto-Van Laere (BVVL) and Fazio-Londe syndromes. BVVL syndrome is characterized by hearing loss and sensory ataxia and causes progressive muscle weakness, optic atrophy, progressive upper limb weakness, bulbar weakness, and sensory ataxia [6].

Riboflavin deficiency may be caused by inborn errors of metabolism. Riboflavin supplementation is a well-accepted therapy in the management of multiple acyl-CoA dehydrogenation deficiency (MADD) and riboflavin transporter deficiencies, leading to significant clinical improvement or stabilization in most patients [7].

RIBOFLAVIN SUPPLEMENTATION IN PREVENTIVE HEALTH CARE

Riboflavin and Migraine Headaches

Riboflavin has been studied as a possible approach to prevention of migraine headaches. Riboflavin is a precursor in the mitochondrial electron transport chain and a cofactor in the Krebs cycle. Greater availability of riboflavin may improve brain mitochondrial function, and riboflavin supplementation reduced the frequency of migraine attacks and the number of headache days [8].

Riboflavin and Cardiovascular Disease

Riboflavin may also play a role in the prevention of cardiovascular disease. High levels of the amino acid homocysteine are associated with an increased risk of cardiovascular disease. Approximately 5% to 30% of the population is homozygous for the genetic variant c.677C>T that is linked to high levels of homocysteine. A daily dose of 1.6 mg of riboflavin for 12 weeks significantly lowered the amount of plasma homocysteine in those homozygous for the c.677C>T variant, possibly decreasing the risk of chronic obstructive pulmonary disease (COPD) [7].

NIACIN

Niacin refers to nicotinamide, nicotinic acid, and the derivatives of these compounds. This vitamin is involved in intracellular respiration and the manufacture of fatty acids [1]. Niacin can donate or accept hydride ions in numerous redox reactions, including intracellular respiration, the oxidation of fuel molecules, and the making of fatty acids [1]. Flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD) are essential cofactors for enzyme-catalyzed reactions [7].

ABSORPTION OF NIACIN

Niacin is primarily absorbed in the small intestines, with a smaller amount absorbed in the stomach [1]. Even when taken in very high doses, niacin is almost completely absorbed. Once absorbed, physiologic amounts of niacin are metabolized to nicotinamide adenine dinucleotide (NAD).

DIETARY NIACIN

Niacin requirements vary by life stage and sex. Boys and men 14 years of age and older require 16 mg/day, while girls and women 14 years of age and older require 14 mg/day. Pregnancy and lactation increase the demand to 18 mg and 17 mg, respectively [1].

Meat, fish, and poultry are rich sources of niacin. Further, whole-grain breads and bread products and ready-to-eat cereals are also niacin sources [1]. Most developed countries fortify flour and cereal products 1–50 mg/niacin per 200 kcal [9]. Tryptophan can be converted to NAD at a low efficiency. Because of this, the concept of niacin equivalents (NE) when determining intake. Total food NE is calculated as the mg niacin plus 1/60 mg tryptophan. Most grains (other than corn, nuts, and legumes) are good sources of NE because they contain a combination of nicotinic acid and tryptophan [9].

EXCESS NIACIN

The upper limit for niacin is 35 mg/day for adults from supplements and fortified foods, but this does not apply to niacin that naturally occurs in food or to tryptophan [9]. Excess niacin intake from fortified food and supplements may cause flushing, nausea and vomiting, liver toxicity, blurry vision, and impaired glucose tolerance [1].

NIACIN DEFICIENCY

Niacin deficiency can result in pellagra, a disease characterized by dermatitis, diarrhea, dementia, and even death. The dementia presents similar to schizophrenia, with hallucinations and delusions, and responds within hours of beginning niacin therapy. The dermatitis results from sun exposure, which suggests a defect in DNA repair [9].

Epidemics of pellagra have been noted in populations that eat mostly corn. Corn is low in tryptophan, and any existing niacin in corn is tightly bound and must be processed with alkali become bioavailable [9].

NIACIN AND CARDIOVASCULAR HEALTH

Niacin has beneficial effects on plasma lipoproteins and clinical benefits in decreasing cardiovascular events and the progression of atherosclerosis [10]. Pharmacological doses of 1–3 g per day of nicotinic acid produce short-term improvements in the ratio of high-density lipoprotein to low-density lipoprotein (HDL:LDL) [9]. Niacin lowers LDL and very-low-density lipoprotein (VLDL) cholesterol, while increasing HDL cholesterol. Niacin inhibits triglyceride synthesis, which in turn results in accelerated intracellular hepatic apolipoprotein B degradation and the decreased secretion of VLDL and LDL particles. Niacin also increases the vascular endothelial cell redox state, thereby inhibiting oxidative stress and the key cytokines involved in atherosclerosis [11].

It is important to note that long-term use of pharmacologic doses of niacin is not recommended. Administration of high doses of niacin over longer periods may increase the risks for skin flushing and itching, sometimes called niacin flush [1; 9]. Prolonged administration may lead to gastrointestinal and musculoskeletal complications and heart failure. Niacin also increases glucose uptake in intestinal cells, thereby leading to increased fasting glucose and potentially causing insulin resistance, new-onset diabetes, and rebound lipid overload [9].

PANTOTHENIC ACID

Pantothenic acid is also called vitamin B5. Its name is derived from the Greek word *pantos*, which means "found everywhere" [12]. Pantothenic acid is a component of coenzyme A, which participates in fatty acid metabolism and is also a component of 4'phosphopaantetheine, both of which must first be hydrolyzed in the intestinal lumen before being absorbed by a sodium-dependent transport mechanism [1]. Pantothenic acid helps make coenzyme A and acyl carrier proteins [13].

ABSORPTION OF PANTOTHENIC ACID

Pantothenic acid is absorbed in the intestine and delivered directly into the bloodstream by active transport (and possibly simple diffusion at higher doses). Pantetheine, the dephosphorylated form of phosphopantetheine, however, is first taken up by intestinal cells and converted to pantothenic acid before being delivered into the bloodstream.

DIETARY PANTOTHENIC ACID

Adequate intake is 5 mg/day for both boys/men and girls/women 14 years of age and older. Pregnant individuals require 6 mg/day, and lactating people need 7 mg/day [1].

Pantothenic acid is widely distributed in foods, including chicken, beef, liver, kidney, egg yolks, potatoes, whole grains, oat cereals, broccoli, and tomatoes [1]. Almonds, peanuts, and peanut butter are also sources, as are wheat bran and cheese [12]. Pantothenic acid is susceptible to oxidation, and large amounts are lost during food processing [13]:

- Refined grains: 37% to 47% loss
- Canned meats: 20% to 30% loss
- Canned vegetables: 46% to 78% loss
- Frozen vegetables: 37% to 57% loss

Pantothenic acid is made by intestinal micro-organisms, although the exact amount is unknown [13].

EXCESS PANTOTHENIC ACID

No adverse effects have been observed with high doses of pantothenic acid. Therefore, pantothenic acid has no upper limit [1].

DEFICIENCY OF PANTOTHENIC ACID

Deficiency of pantothenic acid may manifest as neurological, immunological, hematological, reproductive, and gastrointestinal pathologies. In humans, deficiency causes numbness and burning of feet and hands, headache, insomnia, fatigue, anorexia with gastric disturbances, increased sensitivity to insulin, and impaired antibody production [13].

PANTOTHENIC ACID SUPPLEMENTATION IN PREVENTIVE HEALTH CARE

Pantothenic Acid and Cardiovascular Health

Pantothenic acid may aid in promoting cardiovascular health. When provided in doses of 500–1,200 mg per day, pantetheine, the dimer of pantothenic acid, can lower total serum cholesterol, LDL, and triglycerides and raise HDL in patients with dyslipidemia, hypercholesterolemia, and hyperlipoproteinemia associated with diabetes [13].

Low-grade inflammation, represented by elevated levels of C-reactive protein (CRP), plays an essential role in the early stages of atherosclerosis. Pantothenic acid may have an antioxidant effect. In a study of 908 subjects in South Korea, dietary pantothenic acid was inversely related to subsequent CRP concentration [14].

Pantothenic Acid and Brain Health

Cerebral pantothenate deficiency is a metabolic defect in those with Huntington disease that could possibly impair the synthesis of CoA by neurons, stimulate polyol-pathway activity, impede glycolysis and tricarboxylic acid activity, and alter brain-urea metabolism. However, it is not known whether the metabolic changes in pantothenic acid deficiency themselves cause brain damage, or whether the metabolic problems occur at later states in the pathogenic process and are not involved in neurodegeneration [15]. Treatment involves oral supplementation with high doses of pantothenic acid to replenish the depleted levels in the brain.

VITAMIN B6

Also called pyridoxine, vitamin B6 acts as a coenzyme in more than 150 biochemical reactions [1]. It is active in the metabolism of carbohydrates, lipids, amino acids, and nucleic acids (including DNA and neurotransmitters) and participates in cellular signaling [16; 17]. Vitamin B6 also acts as an antioxidant and may decrease the level of advanced glycation end products in the blood [17]. Vitamin B6 is made up of a group of six related compounds: pyrdoxal (PL), pyrdoxine (PN), pyrdoxamine (PM), and their respective 5'-phosphates, PLD, PNP and PMP. The active form of B6 is pyridoxal phosphate (PLP), which serves as a cofactor for approximately 160 reactions in the body. PLP reduces inflammation in the body by affecting the activity of inflammasomes. PLP also influences the renin-angiotensin systems to control processes such as blood pressure regulation and blood clotting, ensures endothelial integrity, and platelet aggregation [17].

PLP also participates in the transformation of sphingosine-1 phosphate (S1P), formed in platelets but stored in red blood cells. In the red blood cells, PLP is protected against decomposition. S1P is a powerful inflammatory regulator that plays a role in the release of lymphocytes from the lymphoid organs. PLP also acts as a cofactor in the metabolism of tryptophan.

ABSORPTION OF VITAMIN B6

The human body absorbs vitamin B6 in the jejunum. Phosphorylated forms of the vitamin are dephosphorylated, and the pool of free vitamin B6 is absorbed by passive diffusion.

DIETARY VITAMIN B6

The DRI for vitamin B6 in those 14 years of age and older is 1.3–1.7 mg per day [17]. The recommended daily intake is increased in pregnant or lactating patients, to 1.9 mg or 2.0 mg, respectively. Food sources of vitamin B6 include chickpeas, fortified cereals, organ meats (e.g., beef liver), fortified soy-based meat substitutes, starchy vegetables, and some non-citrus fruits (e.g., banana, watermelon) [1].

EXCESS VITAMIN B6

No ill effects of vitamin B6 have been observed with high intakes of the vitamin from food sources. Very large oral doses (2,000 mg/day or higher) of vitamin B6 supplements have been linked to the development of sensory neuropathy and skin lesions [1].

DEFICIENCY OF VITAMIN B6

When PLP is deficient, S1P is inhibited, thereby stopping lymphocytes in lymphatic organs and in places where inflammatory processes occur, leading to immunosuppression, local exacerbation of inflammatory processes, and an increase in the secretion of pro-inflammatory cytokines [17].

VITAMIN B6 SUPPLEMENTATION AND PREVENTIVE HEALTH CARE

Vitamin B6 and Diabetes

Vitamin B6 intake may be inversely related to the progression of diabetes. Vitamin B6 may improve the activity of plasma insulin, thereby decreasing blood glucose. Vitamin B6 also lowers postprandial blood glucose levels after the ingestion of sucrose and starch by inhibiting the activity of small-intestinal α-glucosidases. It is unclear whether diabetes decreases PLP levels or whether low PLP levels trigger diabetes [16].

In the setting of diabetes, a low level of vitamin B6 may increase the risk for cancer. Vitamin B6 ameliorates advanced glycation end products (AGEs) that can contribute to the development of diabetes. As noted, PLP is both an antioxidant and a cofactor for enzymes involved in DNA metabolism. In contrast, PLP deficiency can create DNA damage through the formation of AGEs. In a state of oxidative stress, in which antioxidants are depleted and the means to repair DNA is weak, genotoxic effects may be amplified, thereby increasing the risk for cancer [16].

Vitamin B6 and Premenstrual Syndrome

Premenstrual syndrome (PMS) refers to a variety of physical, emotional, and behavioral symptoms that occur during the luteal phase of the menstrual cycle.

These changes include abdominal cramps, bloating, headache, mood swings, irritability/anger, breast tenderness, and food cravings. A meta-analysis of 12 studies revealed that a daily intake of 100–250 mg of vitamin B6 was more effective than a placebo in reducing physical signs and symptoms of PMS, including abdominal pain, muscle pain, and breast tenderness [18].

Several mechanisms may be responsible for the reduction of PMS symptoms. Because pyridoxine is an immediate precursor of serotonin and dopamine, deficiency may decrease dopamine in the kidneys. This can increase sodium excretion, which in turn creates water retention, leading to edema, swelling in extremities, and discomfort in the chest and abdomen. Also, deficiency may lead to reduced concentrations of noradrenaline and serotonin [18].

FOLATE

Folate is a general term that refers to vitamin B9 that either naturally occurs in food or that occurs in fortified foods and dietary supplements. Folate acts as a coenzyme in the metabolism of nucleic and amino acids.

The requirements for folate are based on dietary folate equivalents (DFEs), which are adjusted for differences in the absorption of folate from foods and supplements. The bioavailability of folate is approximately 50% lower in foods than in supplements [1]. One mcg of DFE is equal to 1.0 mg of folate from food, 0.6 mcg of folate added to food or folate supplement consumed with food, or 0.5 mcg of folate supplement taken on an empty stomach [1]. The recommended daily intake of folate is 400 mcg DFE for persons 14 years of age and older. For pregnant individuals and those who are breastfeeding, the recommended daily intake is 600 mcg DFE and 500 mcg DFE, respectively.

ABSORPTION OF FOLATE

Folate is absorbed in the duodenum and proximal jejunum [19]. Dietary sources of folate are bound to protein in the food and must be freed by digestion or processing before absorption.

DIETARY FOLATE

Folate is naturally present in a wide variety of foods, including vegetables (especially dark green leafy vegetables), fruits and fruit juices, nuts, beans, peas, seafood, eggs, dairy products, meat, poultry, and grains. Spinach, liver, asparagus, and brussels sprouts are among the foods with the highest folate levels. Folate is also produced by intestinal bacteria.

In January 1998, the U.S. Food and Drug Administration (FDA) began requiring manufacturers to add 140 mcg folic acid/100 g to enriched breads, cereals, flours, corn meals, pastas, rice, and other grain products to reduce the risk of neural tube defects. Because cereals and grains are widely consumed in the United States, these products have become important contributors of folic acid to the American diet [20].

EXCESS FOLATE

Large amounts of folate can correct the megaloblastic anemia, but not the neurological damage, that can result from vitamin B12 deficiency. Some experts have therefore been concerned that high intakes of folate supplements might mask vitamin B12 deficiency until its neurological consequences become irreversible [1; 19]. Concerns have also been raised that high folic acid intakes might accelerate the progression of preneoplastic lesions, increasing the risk of colorectal and possibly other cancers in certain individuals [19]. In addition, some scientists have hypothesized that unmetabolized folic acid might be related to cognitive impairment among older adults

DEFICIENCY OF FOLATE

Folate deficiency is the most prevalent vitamin deficiency in the world. In adults, folate deficiency carries numerous risks and can lead to macrocytic anemia, muscle weakness, difficulty walking, and neurological manifestations. High serum levels of homocysteine are an independent risk factor for the development of atherosclerosis. Supplements of 0.5–5.0 mg/day could lower serum homocysteine levels, thereby decreasing the risk of ischemic heart disease by 11% and decreasing stroke risk by 19% [19].

Hereditary folate malabsorption manifests early in life and is characterized by poor feeding, normocytic or macrocytic anemia, pancytopenia, opportunistic infection, behavioral disorders, neuropathy, and seizures. Polymorphism decreases the activity of the MTHFR enzyme, resulting in a decrease in folate concentrations in plasm, serum, and red blood cells [21]. The MTHFR deficit increases the risk of low folate status and high homocysteine levels [19].

Aside from genetic causes, environmental factors can also impact folate levels. Poor dietary intake is the most likely cause, but persons who smoke cigarettes tend to have poor folate status due alterations in the distribution of folate forms [1].

Folate and Neural Tube Defects

Folate is critical for the development of the fetal nervous system and protects against neural tube defects, especially spina bifida [19]. The neural tube forms by 28 days after conception, so supplementation prior to and immediately after conception is vital. The U.S. Public Health Service recommends that all individuals capable of becoming pregnant take 400 mcg of folic acid per day to prevent birth defects [21].

Treatment of Folate Deficiency

There are three main ways to increase folate status. The first is to increase consumption of foods that are naturally high in folate. However, it can be extremely difficult to consume the recommended level of folate from foods alone. As such, a second approach is to increase consumption of foods that are fortified with folic acid. Wheat flour, corn flour, and rice are most typical vehicles for folic acid enrichment. The final approach is to take a folic acid supplement.

INTERACTIONS OF FOLATE WITH OTHER SUBSTANCES

Folate interacts with a number of other dietary substances. Among persons with alcohol use disorder, ethanol intake may worsen folate deficiency by impairing intestinal absorption of folate and increasing folate excretion by the kidneys. Anticonvulsant drugs, such as phenobarbital and diphenylhydantoin, may impair folate status; individuals who take these drugs may require folate supplements [1].

Antifolates are used a class of medications primarily used in the treatment of cancers (e.g., acute myeloid leukemia, lung cancer, osteosarcoma), chronic inflammatory diseases (e.g., rheumatoid arthritis, inflammatory bowel disease), and parasitic and bacterial infections [19]. These drugs cause an intended folate deficiency, and folic acid supplementation may inhibit their action.

Very large doses of nonsteroidal anti-inflammatory drugs (NSAIDs) may also exert antifolate activity. Other medications that inhibit folate include pyrimethamine, trimethoprim, triamterene, trimetrexate, and sulfasalazine [1].

VITAMIN B12

Vitamin B12 is a an essential nutrient found in several foods. Because vitamin B12 contains the mineral cobalt, compounds with vitamin B12 activity are collectively called cobalamins [22]. Methylcobalamin and 5-deoxyadenosylcobalamin are the metabolically active forms of vitamin B12. However, two others forms, hydroxycobalamin and cyanocobalamin, become biologically active after they are converted to methylcobalamin or 5-deoxyadenosylcobalamin.

Vitamin B12 is required for the development, myelination, and function of the central nervous system; healthy red blood cell formation; and DNA synthesis [1]. Vitamin B12 functions as a cofactor for two enzymes: methionine synthase and L-methylmalonyl-CoA mutase. Methionine synthase catalyzes the conversion of homocysteine to the essential amino acid methionine. Methionine is required for the formation of S-adenosylmethionine, a universal methyl donor for almost 100 different substrates, including DNA, RNA, proteins, and lipids [22].

ABSORPTION OF VITAMIN B12

Vitamin B12 is actively absorbed in the stomach and small intestine. Four components are required to absorb vitamin B12: an intact stomach, pancreatic sufficiency, intrinsic factor, and a normally functioning terminal ileum. Vitamin B12 status tends to decline with age due to decreased stomach acidity, atrophic gastritis, and bacterial overgrowth [1].

DIETARY VITAMIN B12

Vitamin B12, also called cobalamin, is naturally found in foods of animal origin; shellfish, organ meats, game meats (e.g., rabbit, venison), and some fish (e.g., herring, sardines, trout) are rich sources [1]. Fortified dairy products and cereals are other potential dietary sources [23].

EXCESS VITAMIN B12

No adverse effects have been observed with high intakes of vitamin B12 in healthy individuals. Even when high doses of B12 are given, the human gastrointestinal tract only absorbs a small percentage [1].

DEFICIENCY OF VITAMIN B12

In humans, the liver can store 4–5 mg of vitamin B12. This amount is sufficient to meet requirements for four to five years. Clinical features of deficiency are evident by five years and include fatigue, shortness of breath, and heart palpitations [23]. Deficiency may also lead to neurological manifestations, including numbness and tingling in the extremities (worse in lower extremities), gait disturbance, and cognitive changes, including memory loss and dementia. Individuals may also have a sore tongue, loss of appetite, constipation, and flatulence [1]. Megaloblastic anemia is a potential hematological effect [23].

The causes of vitamin B12 deficiency are numerous and include pernicious anemia, gastric disease, chronic atrophic gastritis, pancreatic disease, pancreatectomy, resection of the ileum, bacterial overgrowth, or HIV infection. Malnutrition, vegetarianism, or vegan diet may also lead to deficiency [23].

Persons with a deficiency of vitamin B12 may be at greater risk for cardiovascular disease. A high level of homocysteine may result in a shortage of folic acid and vitamin B12. High homocysteine levels have been linked to cardiovascular disease and stroke [23].

Homocysteine is a neurotoxin. Low levels of vitamin B12 contribute to high levels of homocysteine, which causes injury to the brain via oxidative stress [23].

CONCLUSION

The B vitamins are critical for numerous functions in the human body, and deficiency of these important vitamins results in numerous health problems. Practitioners should be careful to counsel patients about meeting the minimum daily requirements of these nutrients via diet and lifestyle. In addition, food fortification and supplements are helpful for increasing intakes.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

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