**VITAMINS AND ESSENTIAL MINERALS….DR TM ADAJA**

**OBJECTIVES**

1. To define vitamins, classify them, and state their functions in humans.
2. To describe the metabolism of vitamin B12, C, A, D, K, B6 ,folate, and their clinical relevances in diseases.
3. To describe laboratory investigations needed to evaluate vitamin deficiencies
4. To interpret case reports in vitamin deficiencies
5. To describe deficiencies and toxicities of various vitamin and their clinical manifestations.

Vitamins are a number of chemically unrelated families of organic substances that cannot be synthesized by humans and are essential in small amounts for normal metabolism. A few are conditionally essential, meaning that they are essential under certain conditions (such as vitamin D, which is thought to be conditionally essential in the absence of adequate sun exposure) Vitamins are divided into water-soluble and fat-soluble vitamins

Many of the vitamin deficiency diseases, such as scurvy (vitamin C), beriberi (thiamine), and pellagra (niacin), have been almost completely eliminated in resource-rich countries except in occasional patients with underlying medical disorders or highly restricted diets. Great interest and controversy continues into whether vitamin supplementation in pharmacologic doses can prevent cancer, heart disease, upper respiratory infections, and other common diseases.

Vitamins play a vital role in many biochemical functions in the human body and are essential components for maintaining optimal health.

There are two main groups of vitamins

– fat-soluble (easily stored in fat upon absorption) and water-soluble (washed out and not easily stored). Although adequate intake of all vitamins is important, regular intake is required to avoid deficiency due to the transient nature of water-soluble vitamins.

The water-soluble vitamins include Vitamin C and Vitamin B complex (thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, biotin, folate, and cobalamin).

Vitamin B complex and vitamin C are found in many foods, especially vegetables and fruits, as well as dairy, meat, legumes, peas, liver, eggs, and fortified grains and cereals. In addition to serving as cofactors in biochemical reactions, the vitamin B complex is vital for normal body growth and development, healthy skin, the proper function of nerves and the heart, and red blood cell formation. The overall lack of water-soluble vitamins is rare in North America, though it can present in alcohol use disorder, malabsorption syndromes, strict veganism, and malnourished states

**Issues of Concern**

As stated above, the deficiency of water-soluble vitamins is rare in North America. However, deficiency may be a presenting feature in alcohol use disorder, malnourishment, and malabsorption syndromes such as short-bowel syndrome.

 In short-bowel syndrome, there is the removal of a large portion of the small intestine for various reasons such as Crohn disease, necrotizing enterocolitis, traumatic injury, obstruction, or cancer. The small bowel is the site of absorption for all vitamins, and if a significant portion is surgically removed (typically enough so that less than or equal to 200 cm of bowel remains), the body will be unable to absorb vitamins adequately. Treatment includes vitamin supplementation.

**Testing**

Although it is tempting to simply obtain urine or serum levels of water-soluble vitamins, these reflect only presently circulating vitamin levels and cannot approximate storage levels. Alternate forms of testing **include immunoassays, chromatographic methods, chemical methods, high-pressure liquid chromatography, and capillary electrophoresis, depending on the vitamin being tested**.

For vitamin B12 (cyanocobalamin) and folate deficiency, as discussed below, it is essential to obtain a complete blood cell count  (checking MCV, hematocrit, and hemoglobin) in addition to methylmalonic acid and homocysteine level.

**Clinical Significance**

Vitamins are classified into two categories based on how they are absorbed and if they are stored. Water-soluble vitamins dissolve in water upon entering the body. Because of this, humans cannot store excess amounts of water-soluble vitamins for later use.

There are nine water-soluble vitamins: the B vitamins -- folate, thiamine, riboflavin, niacin, pantothenic acid, biotin, vitamin B6, and vitamin B12 -- and vitamin C.

 Deficiency of any of these water-soluble vitamins results in a clinical syndrome that may result in severe morbidity and mortality.

* **Thiamine (B1)** is a cofactor (TPP) for multiple enzymes, including pyruvate dehydrogenase, alpha-ketoglutarate, transketolase, and branched-chain ketoacid dehydrogenase, all of which are involved in glucose breakdown. Deficiency can result in adenosine triphosphate (ATP) depletion and often affects highly aerobic tissues such as the brain, nerves, and heart first. With heart involvement, it is called **wet beriberi** and is characterized by high-output heart failure, edema, and dyspnea on exertion. When the nervous system is involved, it is called **dry beriberi**, characterized by polyneuritis and symmetrical muscle wasting. Damage to the medial dorsal nucleus of the thalamus and the mammillary bodies in the brain can result in a condition called **Wernicke encephalopathy**, recognized by the classic triad of confusion, ophthalmoplegia, and ataxia, or Wernicke-Korsakoff syndrome when accompanying confabulation, personality change, and memory loss is present. Thiamine deficiency often is part of the presentation in patients with alcohol use disorder secondary to malnutrition and malabsorption, in addition to patients suffering from malnutrition.
* **Riboflavin (B2)** is a cofactor in redox reactions (FAD and FMN). Deficiency leads to **cheilosis** (inflammation of lips and fissures of the mouth) and corneal vascularization. Of note, ultraviolet (UV) light can destroy riboflavin; hence it is always packaged in opaque containers.
* **Niacin (B3)** is also utilized in redox reactions (as NAD+ and NADP+) and derives from tryptophan. Deficiency can present as **pellagra**, otherwise known as **the 3-D’s: diarrhea, dermatitis, and dementia**. Deficiency is rare in the USA but can occur in alcoholics and those with malnutrition. Niacin can be used to treat dyslipidemia, and a side effect is facial flushing, which can be avoided by treatment with aspirin.
* **Pantothenic acid (B5)** is a component of coenzyme A and fatty acid synthase, both of which are necessary for energy production and the formation of hormones. Deficiency is characterized by **dermatitis, enteritis, alopecia, and adrenal insufficiency**.
* **Pyridoxine (B6)** is converted to pyridoxal phosphate (PLP) and is part of reactions including ***transamination, decarboxylation, and glycogen phosphorylase***. It is critical for the formation of red blood cells, and deficiency can result in sideroblastic anemia, hyperirritability, convulsions, peripheral neuropathy, and mental confusion. Peripheral neuropathy is a potential side effect of isoniazid, a key drug utilized in treating tuberculosis, and it is customary to supplement treatment with B6.
* **Biotin (B7)** is necessary for the metabolism of protein, fats, and carbohydrates. Deficiency can lead to **muscle pain, heart problems, anemia, and depression.** Additionally, since biotin is a contributor to keratin, biotin has become popularized as a supplement to improve the quality of hair, skin, and nails. Large, unregulated doses of biotin can skew a variety of clinical tests, including thyroid tests T3 and T4, which can be either falsely elevated or falsely lowered depending on the particular assay; this is because nearly all immunoassays rely on the biotin-streptavidin attraction. This binding is also responsible for the biotin deficiency seen as a result of chronic consumption of large amounts of raw egg whites, as raw egg whites contain a high volume of intact avidin, which strongly binds biotin. When egg whites are cooked, the avidin denatures and does not bind biotin as avidly. Of note, TSH levels are unaffected by biotin supplementation.
* **Folate (B9)** is converted to tetrahydrofolate and is vital for DNA and RNA synthesis. Deficiency can result in neural tube defects, prompting folate supplementation during pregnancy, and macrocytic (MCV>100) megaloblastic anemia. Folate deficiency may also be a feature of alcohol use disorder.
* **Cobalamin (B12)** is essential for erythropoiesis and the growth of the nervous system. Deficiency may lead **to pernicious anemia and subacute combined degeneration of the spinal cord.** The ***macrocytic megaloblastic anemia from B12 deficiency presents similarly to folate deficiency, and to differentiate them, it is imperative to obtain serum homocysteine and methylmalonic acid levels***. **In folate deficiency, homocysteine will elevate, but methylmalonic acid levels will be normal. In vitamin B12 deficiency, both homocysteine and methylmalonic acid levels will present as elevated**. **Additionally, B12 deficiency will present with neurologic symptoms, whereas folate deficiency will not.**
* **Vitamin C (ascorbic acid, ascorbate**) is needed for collagen growth, wound healing, bone formation, enhancing the immune system, absorption of iron, strengthening blood vessels, and acting as an antioxidant. When deficiency occurs, it can result in scurvy which can present with swollen and bleeding gums, loss of teeth, poor wound healing, and poor tissue growth.

|  |  |  |
| --- | --- | --- |
| Nutrient | Function | Sources |
| Thiamine (vitamin B1) | Part of an [enzyme](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=ste122090&lang=en-ca#ste122090-sec) needed for energy metabolism; important to nerve function | Found in all nutritious foods in moderate amounts: pork, whole grain foods or enriched breads and cereals, legumes, nuts and seeds |
| [Riboflavin](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=str15675&lang=en-ca#str15675-sec) (vitamin B2) | Part of an enzyme needed for energy metabolism; important for normal vision and skin health | Milk and milk products; leafy green vegetables; whole grain foods, enriched breads and cereals |
| Niacin (vitamin B3) | Part of an enzyme needed for energy metabolism; important for nervous system, digestive system, and skin health | Meat, poultry, fish, whole grain foods, enriched breads and cereals, vegetables (especially mushrooms, asparagus, and leafy green vegetables), peanut butter |
| Pantothenic acid | Part of an enzyme needed for energy metabolism | Widespread in foods |
| Biotin | Part of an enzyme needed for energy metabolism | Widespread in foods; also produced in intestinal tract by bacteria |
| Pyridoxine (vitamin B6) | Part of an enzyme needed for protein metabolism; helps make [red blood cells](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=tv7033&lang=en-ca#tv7033-sec) | Meat, fish, poultry, vegetables, fruits |
| [Folic acid](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=stf15552&lang=en-ca#stf15552-sec) | Part of an enzyme needed for making [DNA](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=std120898&lang=en-ca#std120898-sec) and new cells, especially red blood cells | Leafy green vegetables and legumes, seeds, orange juice, and liver; now added to most refined grains |
| Cobalamin (vitamin B12) | Part of an enzyme needed for making new cells; important to nerve function | Meat, poultry, fish, seafood, eggs, milk and milk products; not found in plant foods |
| Ascorbic acid (vitamin C) | [Antioxidant](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=sta123283&lang=en-ca#sta123283-sec); part of an enzyme needed for protein metabolism; important for immune system health; aids in iron absorption | Found only in fruits and vegetables, especially citrus fruits, vegetables in the cabbage family, cantaloupe, strawberries, peppers, tomatoes, potatoes, lettuce, papayas, mangoes, kiwifruit |

Only vitamins A, E, and B12 are stored to any large extent in the body.

VITAMIN A: An important fat-soluble vitamin, vitamin A’s basic molecule is a retinol, or vitamin A alcohol. After absorption, retinol is transported via chylomicrons to the liver, where it is either stored as retinol ester or reexported into the plasma in combination with retinol-binding protein for delivery to tissue sites.

Dietary vitamin A is obtained from preformed vitamin A (or retinyl esters), which is found in animal foods (liver, milk, kidney, fish oil), fortified foods, and drug supplements. Dietary vitamin A is also obtained from provitamin A carotenoids from plant sources, principally carrots. Dietary vitamin A is available mainly as preformed vitamin A in western countries and as provitamin A carotenoids in developing countries.

Supplements are typically 10,000-50,000 international units (IU) per capsule. Fish-liver oils may contain more than 180,000 IU/g. The acute toxic dose of vitamin A is 25,000 IU/kg, and the chronic toxic dose is 4000 IU/kg every day for 6-15 months. (Beta-carotene [ie, provitamin A] is converted to retinol but not rapidly enough for acute toxicity.) Being fat-soluble, vitamin A is stored to a variable degree in the body, making it more likely to cause toxicity when taken in excess amounts.In contrast, water-soluble vitamins are generally excreted in the urine and stored only to a limited extent; hence, adverse effects occur only when extremely large amounts are taken.

The bioavailability of retinol is generally more than 80%, whereas the bioavailability and bioconversion of carotenes (ie, provitamin A) are lower. These may be affected by species, molecular linkage, amount of carotene, nutritional status, genetic factors, and other interactions.

While in general the body absorbs retinoids and vitamin A very efficiently, it lacks the mechanisms to destroy excessive loads. Thus, the possibility of toxicity exists unless intake is carefully regulated.It has been suggested that earlier estimates of daily human requirements of vitamin A be revised downward. [15]

Vitamin A is highly teratogenic in pregnancy, especially in the first 8 weeks with daily intake more than 10,000 IU; however, it is also a cofactor in night vision and bone growth.

[Carotenemia](http://emedicine.medscape.com/article/1104368-overview) is the result of excessive intake of vitamin A precursors in foods, mainly carrots. Other than the cosmetic effect, carotenemia has no adverse consequences, because the conversion of carotenes to retinol is not sufficient to cause toxicity.

Isotretinoin (Accutane), a drug used for the treatment of severe forms of acne, is closely related to the chemical structure of vitamin A, which means that the pharmacology and toxicology of these two compounds are similar. Birth defects (when taken during pregnancy), intracranial hypertension, depression, and suicidal ideation have been reported with isotretinoin. [16] A careful drug history to uncover this possibility of isotretinoin use is important in patients presenting with manifestations suggestive of vitamin A intoxication.

* Vitamin A supports healthy eyesight and immune system functions. Children with vitamin A deficiency face an increased risk of blindness and death from infections such as measles and diarrhea6.
* Globally, vitamin A deficiency affects an estimated 190 million preschool-age children6.
* Providing vitamin A supplements to children ages 6-59 months is highly effective in reducing deaths from all causes where vitamin A deficiency is a public health concern6.

VITAMIN D: Vitamin D (ie, cholecalciferol) is present in most dairy products, egg yolks, liver, and fish. It increases serum calcium levels by facilitating calcium absorption and mobilizing calcium from bone. Supplements usually are 400 IU per tablet. The RDAs for vitamin D are as follows:

* Age 0-12 months (adequate intake) - 10 mcg (400 IU)
* Age 1-70 years (including lactation and pregnancy) - 15 mcg (600 IU)
* Age > 70 years - 20 mcg (800 IU)
* Vitamin D builds strong bones by helping the body absorb calcium7. This helps protect older adults from osteoporosis.
* Vitamin D deficiency causes bone diseases, including rickets in children and osteomalacia in adults7.
* Vitamin D helps the immune system resist bacteria and virsues7.
* Vitamin D is required for muscle and nerve functions7.
* Available data suggest that vitamin D deficiency may be widespread globally8.
* Bodies make vitamin D from sunlight, but this varies based on geography, skin color, air pollution, and other factors. Also, sunlight exposure needs to be limited to [avoid risk of skin cancer](https://www.cdc.gov/cancer/skin/basic_info/sun-safety.htm).
* All children need [vitamin D](https://www.cdc.gov/nutrition/InfantandToddlerNutrition/vitamins-minerals/vitamin-d.html) beginning shortly after birth.
* <https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/> \****OPTIONAL BUT READ IT***

VITAMIN E: Vitamin E is any of a group of at least 8 related fat-soluble compounds with similar biological antioxidant activity, particularly alpha-tocopherol but also including other isomers of tocopherol and the related compound tocotrienol. Vitamin E is found in vegetable oil, nuts, sunflower, wheat, green leafy vegetables, and fish. It is a fat-soluble vitamin that acts as an antioxidant and free-radical scavenger in lipophilic environments. Bile is required for absorption; 25% of vitamin E is absorbed orally. Storage of the vitamin occurs in adipose tissue, the liver, and muscle.

Vitamin E may block absorption of vitamins A and K. In addition, it decreases low-density lipoprotein (LDL) cholesterol level at doses more than 400 IU/day.

One milligram of synthetic vitamin E (all-rac-alpha-tocopherol acetate) is equivalent to 1 IU of vitamin E. One milligram of natural vitamin E (RRR–alpha tocopherol) is equivalent to 0.45 IU of vitamin E.

In a 2000 report, the Food and Nutrition Board of the National Academy of Sciences specified the RDA of vitamin E as 15 mg/day and listed the tolerable upper intake level (UL) of any alpha-tocopherol form as 1000 mg/day (1500 IU/day). The UL is the upper level that is likely to pose no risk of adverse health effects to almost all people in the general population.

While in most healthy adults, short-term supplementation with up to 1600 IU of vitamin E appears to be well tolerated and have minimal side effects, the long-term safety is questionable.Data suggest a possible increase in mortality and in the incidence of heart failure with long-term use of vitamin E (400 IU or more), especially in patients with chronic diseases.Therefore, a UL of 1000 mg/day may be too high, especially if only the alpha-tocopherol form of vitamin E is used (vitamin E consists of 8 compounds and supplementing only one form can be detrimental). Supplements usually are 100-1000 IU per capsule.

The RDAs for vitamin E are as follows

* Age 14 years and older - 15 mg
* Pregnancy (14 y and older) - 15 mg
* Lactation (14 y and older) - 19 mg

The RDAs for children are as follows:

* Age 0-6 months (adequate intake) - 4 mg
* Age 7-12 months (adequate intake) - 5 mg
* Age 1-3 years - 6 mg
* Age 4-8 years - 7 mg
* Age 9-13 years - 11 mgM

VITAMIN K: Vitamin K (ie, phytonadione) is produced by intestinal bacteria (vitamin K-2) and is found in green, leafy vegetables; cow's milk; and soy oil (vitamin K-1). Vitamin K-1 supplements are usually 2.5-10 mg. Phytonadione promotes liver synthesis of factors II, VII, IX, and X.

Measured in terms of adequate intake (as opposed to RDA), the recommendations for daily intake of vitamin K are as follows:

* Age 19 years or older (males) - 120 mcg
* Age 19 years or older (females) - 90 mcg
* Pregnancy and lactation (19-50 y) - 90 mcg

Adequate intakes in children are as follows:

* Age 0-6 months - 2 mcg
* Age 6-12 months - 2.5 mcg
* Age 1-3 years - 30 mcg
* Age 4-8 years - 55 mcg
* Age 9-13 years - 60 mcg
* Age 14-18 years - 75 mcg (including pregnancy and lactation)

|  |  |  |
| --- | --- | --- |
| Nutrient | Function | Sources |
| Vitamin A (and its precursor\*, beta-carotene)\*A precursor is converted by the body to the vitamin. | Needed for vision, healthy skin and mucous membranes, bone and tooth growth, immune system health | Vitamin A from animal sources (retinol): fortified milk, cheese, cream, butter, fortified margarine, eggs, liverBeta-carotene (from plant sources): Leafy, dark green vegetables; dark orange fruits (apricots, cantaloupe) and vegetables (carrots, winter squash, sweet potatoes, pumpkin) |
| Vitamin D | Needed for proper absorption of [calcium](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=stc123615&lang=en-ca#stc123615-sec); stored in bones | Egg yolks, liver, fatty fish, fortified milk, fortified margarine. When exposed to sunlight, the skin can make vitamin D. |
| Vitamin E | Antioxidant; protects cell walls | Polyunsaturated plant oils (soybean, corn, cottonseed, safflower); leafy green vegetables; wheat germ; whole-grain products; liver; egg yolks; nuts and seeds |
| Vitamin K | Needed for proper blood clotting | Leafy green vegetables such as kale, collard greens, and spinach; green vegetables such as broccoli, Brussels sprouts, and asparagus; also produced in [intestinal](https://myhealth.alberta.ca/Health/pages/conditions.aspx?hwid=sti150710&lang=en-ca#sti150710-sec) tract by bacteria |
|  |  |  |

Some [**minerals**](https://www.msdmanuals.com/home/disorders-of-nutrition/minerals/overview-of-minerals) are required in fairly large quantities (about 1 or 2 grams a day) and are considered macronutrients. They include calcium, chloride, magnesium, phosphorus (occurring mainly as phosphate in the body), potassium, and sodium.

Minerals required in small amounts (trace minerals) are considered micronutrients.

They include chromium, copper, fluoride, iodine, iron, manganese, molybdenum, selenium, and zinc.

 **Except for chromium, all of these minerals are incorporated into enzymes or hormones required in metabolism. Chromium helps the body keep blood sugar levels normal.**

Trace minerals such as arsenic, cobalt, fluoride, nickel, silicon, and vanadium, which may be essential in animal nutrition, have not been established as requirements in human nutrition. Fluoride helps stabilize the mineral content of bones and teeth by forming a stable compound with calcium and thus helps prevent tooth decay.

 All trace minerals are toxic at high levels, and some (arsenic, nickel, and chromium) can cause cancer.

* ZINC: Zinc promotes immune functions and helps people resist infectious diseases including diarrhea, pneumonia and malaria. Zinc is also needed for healthy pregnancies14.
* Globally, 17.3% of the population is at risk for zinc deficiency due to dietary inadequacy; up to 30% of people are at risk in some regions of the world17.
* Providing zinc supplements reduces the incidence of premature birth, decreases childhood diarrhea and respiratory infections, lowers the number of deaths from all causes, and increases growth and weight gain among infants and young children.
* Providing zinc supplementation to children younger than 5 years appears to be a highly cost-effective intervention in low- and middle-income countries
* When children are about 6 months old, it is important to start giving them [foods with zinc](https://www.cdc.gov/nutrition/infantandtoddlernutrition/vitamins-minerals/zinc.html).
* **IODINE**: Iodine is required during pregnancy and infancy for the infant’s healthy growth and cognitive development9.
* Globally an estimated 1.8 billion people have insufficient iodine intake.
* Iodine content in most foods and beverages is low.
* Fortifying salt with iodine is a successful intervention – about 86% of households worldwide consume iodized salt10. The amount of iodine added to salt can be adjusted so that people maintain adequate iodine intake even if they consume less salt11.
* The American Thyroid Association and the American Academy of Pediatrics recommend that pregnant or breastfeeding women take a supplement every day containing 150 micrograms of iodine. The American Thyroid Association recommends women who are planning a pregnancy consume a daily iodine supplement starting at least 3 months in advance of pregnancy.

## Antioxidants

Some vitamins (such as vitamins C and E) and minerals (such as selenium) act as antioxidants, as do other substances in fruits and vegetables (such as beta-carotene).

Antioxidants protect cells against damage by free radicals, which are by-products of the normal activity of cells. Free radicals readily participate in chemical reactions—some useful to the body and some not—and are thought to contribute to such disorders as heart and blood vessel disorders and cancer. People who eat enough fruits and vegetables, which are rich in antioxidants, are less likely to develop heart and blood vessel disorders and certain cancers. However, whether these benefits are due to antioxidants, other substances in the fruits and vegetables, or other factors in people's diet and lifestyle is not known; also, taking antioxidant supplements has not been shown to prevent disease or mortality and sometimes can cause harm.

## Supplements

Getting enough vitamins and minerals from foods is usually preferable to getting them from supplements. Foods, unlike supplements, contain other substances necessary for good health. However, always eating a healthy, well-balanced diet may be difficult. So taking a multivitamin that contains the recommended daily allowances for vitamins and minerals may be a good idea, particularly when a healthy diet may not be possible.**THE END**

**DR TM ADAJA**