REVIEW

DEFICIENCY AND TOXICITY OF VITAMINS

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Abstract: Vitamins are substances necessary to sustain life, with many functions. Vitamins must be obtained from food, as they are either not made in the body at all or are not made in sufficient quantities for growth, vitality and wellbeing. Lack of a particular vitamin can lead to incomplete metabolism, fatigue and other important health problems. Deficiency of a vitamin causes symptoms which can be cured by that vitamin. Large doses of vitamins may slow or ever reverse diseases such as cancer, osteoporosis, nerve degeneration and heart disease.

Keywords: vitamins, deficiency, excess, water-soluble vitamins, fat-soluble vitamins.

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Abreviations: ACP-acyl carrier protein CRP- C-reactive protein; DRI-dietary reference intake; GPX-3-Glutathione peroxidase 3; G6PD-Glucose-6-phosphate dehydrogenase; EAR-estimated average requirement; Holo-TC-holo-transcobalamin; HPLC-high-pressure liquid chromatography; MMA-methylmalonic acid; NAD-nicotinamide adenine dinucleotide; RDA-reccomended dietary allowance; ThDP-thiamine diphosphate; VKDp -vitamin K dependent-proteins.

INTRODUCTION

Vitamins are substances which are necessary to sustain life. They are divided in water-soluble vitamins (B-complex) and fat-soluble vitamins (vitamin A, vitamin D, vitamin K and vitamin E). Vitamins are essential for the normal function of human body metabolism. They play a role in metabolism enabling the body to use other essential nutrients such as carbohydrates, fats, proteins and minerals. Individual vitamins have specific functions which vary widely and can overlap. They are involved in growth and the maintenance of health and are important for a normal appetite, in digestion and resistance to bacterial infections. It is important to understand that vitamins are not substitutes for food.

THIAMINE (VITAMIN B1)

Thiamine is a water-soluble vitamin essential for carbohydrate metabolism and energy metabolism [1]. Body stores of thiamine are limited and dependent on dietary intake. There are five natural thiamine phosphate derivatives.

The absorption of vitamin B1 occurs in the jejunum and ileum and it can be inhibited by

alcohol consumption and folate deficiency. The EAR for women and men are 0.9-1 mg/day [2], [3]. Enteral nutrition should provide 1.5-3 mg/day and parenteral nutrition at least 2.5 mg/day of thiamine.

The main sources of vitamin B1 are whole grains, legumes, meats, nuts and fortified foods. Thiamine reserves are depleted in 20 days of inadequate oral intake. Patients at risk of deficiency include malnutrition, poor oral intake and chronic alcohol consumption, malignancies and pregnancy. Reduced gastrointestinal absorption and increased gastrointestinal or renal losses and obesity pre-bariatric surgery should be considered [3]. Critical illness like sepsis and major trauma are associated with thiamine deficiency or depletion.

Thiamine status may be determined using indirect and direct methods. Erythrocyte transketolase activity is an indirect method, while direct methods include the quantification of ThDP, the coenzyme of thiamine in whole blood or red blood cells.

Thiamine deficiency symptoms include neurological, psychiatric and cardiovascular systems [1], [4]. Apathy, decrease in short-term memory, confusion and irritability to cognitive deficits and Wernicke-Korsakoff encephalopathy, optic neuropathy, Leigh's disease, African Seasonal Ataxia and central pontine myelinolysis [5]. Vitamin B1 can be administred by oral, enteral and intravenous routes and is cheap all over the world. There is no toxicity of thiamine.

RIBOFLAVIN (VITAMIN B2)

Riboflavin is also a water-soluble vitamin and is involved in redox reactions, antioxidant functions, metabolism of the other B vitamins and energy production. It has several immunomodulatory effects.

Absorption takes place in the proximal small intestine and it is also produced by the microflora of the large intestine. Riboflavin is excreted in the urine and it is not stored in the body [6].

Main sources: enriched and fortified grains, cereals and bakery products, meats, fatty fish and eggs [7]. The RDA is 1,3 mg/day in men, 1.1 mg/day in women and 1.4 mg and 1.6 mg during pregnancy and lactation. The riboflavin status can be assessed by the glutathione reductase activity in red blood cells [6].

Deficiency of riboflavin is manifested by oral lesions, seborrheic dermatitis of the face, trunk and scrotum, ocular symptoms and normochromic, normocytic anemia and marrow aplasia. Patients at risk are those with malabsorption, thyroid dysfunction, diabetes, alcoholism and in pregnancy, lactation, patients with surgery, trauma, burs and patients on psychotropic drugs, tricyclic antidepressants or barbiturates. Riboflavin deficiency is associated with pyridoxine, folate and niacin deficiency [6], [7]. Toxicity of vitamin B2 is rare.

NIACIN (VITAMIN B3)

The metabolically active form of niacin is the coenzyme NAD. Niacin helps to convert nutrients into energy, create cholesterol and fats, create and repair DNA. Niacin can be synthesized from the amino acid tryptophan in the liver, a pathway which also requires thiamine, riboflavin and pyridoxine. Blood or tissue NAD can be used for the assessment of niacin [2], [7].

Main sources: processed foods, meat, poultry, red fish, nuts, legumes and seeds. Adolescent and adults intake is 16 mg/day (males), 14 mg/day (females) and 18 mg/day (pregnant women) [8],[9]. Enteral nutrition should provide 18-40 mg/day and parenteral nutrition should provide 40 mg/day of this vitamin.

Primary niacin deficiency occurs on a corn-based diet and in general malnutrition. Secondary causes include chronic alcoholism and prolonged diarrhea. "Pellagra" or "the three D disease" is characterized by diarrhea, dermatitis and dementia. Other causes of deficiency are inadequate oral intake, defective tryptophan absorption, carcinoid

tumors and chemotherapeutic treatments [10], [11], [12]. A prospective population-based study suggested that dietary niacin protects against Alzheimer disease and age-related cognitive decline [13].

Flushing in the face, arms and chest and hepatotoxicity are symptoms of toxicity. Hepatitis can be produces by energy drinks that contain large quantities of niacin [14].

PANTOTHENIC ACID (VITAMIN B5)

Pantothenic acid is part of the coenzyme A and acyl carrier protein. It is involved in oxidative respiration, lipid metabolism and synthesis of steroids. 85% of vitamin B5 exists as derivatives such as coenzyme A phosphopantetheine and ACP which are converted to pantothenic acid by pancreatic enzymes [15]. It is absorbed along the small intestine.

The DRI is 5 mg/day and the needs increase to 6-7 mg/day for pregnant and lactating women [2]. Enteral nutrition should provide 5 mg/day and parenteral nutrition should provide 15 mg/day of vitamin B5 along with other B-vitamins.

The sources are fortified cereals, organ meats, beef, chicken, avocado, nuts and milk products.

Deficiency of pantothenic acid was observed only in conditions of severe malnutrition. Symptoms of deficiency include fatigability, frequent upper respiratory infections, but severe deficiency may lead to headache, extreme tiredness, irritability, sleeping problems, nausea and vomiting [16]. Cerebral pantothenate deficiency is a newly identified metabolic defect in Huntington and Alzheimer diseases [17]. In context of neurological symptoms, pantothenic acid blood determination should be performed. Derivative of pantothenic acid is often used as a source of vitamin in vitamin supplements. Calcium pantothenate is used in dietary supplements because, as a salt, is more stable than pantothenic acid. Pantothenic acid supplementation might reduce lipid levels in patients with hyperlipidemia because of the role in triglygeride syntehesis and lipoprotein metabolism.

No toxicity of vitamin B5 has been reported.

PYRIDOXINE (VITAMIN B6)

Pyridoxal phosphate (PLP) is the biologically active form of pyridoxine which serves as coenzyme for more than 160 enzymatic reactions (transamination, racemization, decarboxylation). The most important role of vitamin B6 is related to the biosynthesis as the degradation of amino acids, is central to transamination reactions. Other functions are gluconeogenesis, steroid receptor binding and heme biosynthesis [19].

Absorption of pyridoxine occurs in the small bowel. The DRI is 1.3-1.7 mg/day for men and women. The need can reach 2 mg/day for pregnant women. Normal values of PLP are 5-50 μg/L [2].

Diet is the only source of vitamin B6. Sources of pyridoxine are meat, whole grains and potatoes. Plasma levels of pyridoxal 5-phosphate correlate with pyridoxine intake and body stores and is recognized as a status biomarker. PLP may be determined in plasma, serum and erythrocytes [20].

Inflammation leads to a fall in plasma PLP, but minimally affects red blood cell concentrations. Symptoms of pyridoxine deficiency include seborrheic dermatitis with cheilosis and glossitis, microcytic anemia, confusion, depression and angular stomatitis [21]. Causes of deficiency are isoniazid therapy, HIV infection therapy and treatment, alcoholic hepatitis, migraine attacks and thymoglobulin immunosuppression for organ transplantation. Pyridoxine-dependent epilepsy is a rare autosomal recessive epileptic encephalopathy caused by antiquitin deficiency. Population at risk of deficiency include alcoholics, renal dialysis patients, the elderly, critical illness, pregnancy and people receiving medical therapies that inhibit vitamin activity [18], [22], [23], [24].

Sensory neuropathy with ataxia or areflexia, impaired cutaneous and deep

sensations and dermatological lesions are clinical signs of excess pyridoxine. Long-term doses as low as 100 mg/day have been associated with spinal cord affections [25]. In context of isoniazid overdose or glycol poisoning, high dose of pyridoxine should be used as part of the treatment.

BIOTIN (VITAMIN B7)

Also, a water-soluble vitamin, biotin can be found in all cells of human body. Main functions of this vitamin include: metabolism of the fatty acids, glucose and amino acids as it is a cofactor for five carboxylases critical for their metabolism. Biotin is an essential vitamin for normal fetal development [26].

Healthy adults need 40 μg/day and lactating women 45 μg/day. The Institute of Medicine recommends 30 μg/day plus additional 5 μg/day for lactating women. Vitamin B7 can be administered by oral and intravenous routes. Enteral nutrition should provide 30 μg/day and parenteral nutrition 60 μg/day of vitamin B7 [26], [27].

Biotin sources: egg yolks, milk, organ meats and multivitamin supplements. For vegans main sources of biotin are peanuts, avocado, sweet potatoes and tomatoes. Biotin status has to be determined by the direct measure of blood and urine level of biotin and should be completed by the determination of biotindinase activity.

Deficiency of biotin is rare, but when is present leads to dermal and neurological complications. Causes of deficiency include chronic alcohol consumption, malabsorption in Chron's disease, smoking and pregnancy [28], [29]. Anticonvulsant therapy can interfere with the absorption of vitamin B7 and increase needs, but more recent data suggest that there is no concern about valproate and carbamazepine [30].

No adverse effects of biotin pharmacological doses have been shown.

FOLATE AND FOLIC ACID (VITAMIN B9)

The biologically active folate forms are folinic acid and 5-methyltetrahydrofolate (5-MTHF). Folate has an important role as cofactor in the metabolism of nucleic acid precursors and several amino acids [31].

Absorption of folates occurs in the duodenum and jejunum in a pH-dependent carrier-mediated process. Folic acid is manufactured synthetically and is available in supplements or fortified foods: it is converted in the body into folate [32].

Sources of folate: egg, nuts, whole grain products and green vegetables. The DRI varies from 250 to 400 μg/day. Pregnant and lactating women needs are about twice as high [33], [34]. Folic acid may be administered orally, enteral, subcutaneous, intravenous and intramuscular. Enteral nutrition should provide 330-400 μg/day and parenteral nutrition 400-600 μg/day of folic acid. Folate status shall be assessed in plasma or serum (short-term status) or red blood cells (long-term-status). Red blood cells folate level is a sensitive marker of long-term folate status because it informs about folate accumulation during red cell erythropoiesis as well as tissue folate stores.

Folate deficiency overlap with cobalamin deficiency. Symptoms include glossitis, angular stomatitis, oral ulcers, depression, insomnia, anorexia and fatigue. Deficiency of both vitamins causes megaloblastic anemia [35]. Causes of folate deficiency may be inadequate dietary intake (poverty poor nutrition), intestinal malabsorption (celiac disease, chronic intestinal failure), increased needs (pregnancy and lactation, neoplastic diseases, renal dialysis) and antifolate drugs (sulfasalazine, methotrexate, anticonvulsants). In case of dietary deficiency or chronic hemodialysis 1-5 mg folic acid/day may be given orally.

Folic acid has proliferative effects so it might increase cancer risk and progression. It is said that folic acid can cause insulin resistance in children, mask a vitamin B12

deficiency and be hepatotoxic [36]. Excess folic acid is excreted in the urine.

1. COBALAMIN (VITAMIN B12)

Cobalamin is a water-soluble vitamin synthesized by fungi and microorganism and in the stomach of ruminant animals dependent on soil cobalt content. Humans are totally dependent upon animal sources of fortification [37], [38].

Cobalamin absorption has several steps, and it requires normal stomach, pancreas and small intestine function. Vitamin B12 is a cofactor for two enzymes in humans: methionine synthase in methyl transfer from methyl tetrahydrofolate to form methionine from homocysteine and methyl malonyl-coA mutase in synthesis of the citric acid cycle intermediate succinyl coA [38].

The main sources of vitamin B12 are ruminant meat, organs, milk, fish, fortified cereals and nutritional yeast. The DRI for adults is 2,4 μg/day. In pregnancy the needs are 5 μg/day and in lactation 4,5 μg/day. In adults, vitamin B12 reserves are approximately 2500 μg and it may last for 12-36 months without sufficient intake [89]. Enteral nutrition should provide 2.4 μg/day and parenteral nutrition 5 μg/day of cobalamin.

The main cause of low serum cobalamin in younger adults is inadequate intake because of low consumption of animal-sources [39]. The most common causes of deficiency are an autoimmune condition as pernicious anemia, food-bound cobalamin malabsorption and chronic atrophic gastritis. Primarily, the manifestations are haematological and neuropsychiatric deterioration. Clinical symptoms include macrocytosis, reticulocytosis, anemia with pallor, fatigue, tachycardia, peripheral neuropathy, paresthesia, tingling, vertigo, ataxia, irritability, psychosis, depression, confusion, cognitive decline, dementia, glossitis, and weakness. It is very important that vitamin B12 deficiency be excluded in all patients who present with anemia or isolated macrocytosis, established diagnosis of polyneuropathies, neurodegenerative diseases or psychosis.

There is no upper toxicity limit for cobalamin and no reports of acute toxicity, but cobalamin excess with high blood levels has been observed in alcoholism, liver disease and cancer [40].

Adults at risk or suspected of cobalamin deficiency should be screened with the combination of at least two markers (holo-TC, MMA) with serum cobalamin as a replacement.

VITAMIN A

There are two different active metabolites of vitamin A: retinoic acid and retinal which are responsible for vision and reproductive function [41]. It also has an important role in the immune system. Retinol binding protein is a negative acute phase protein which leads to a fall serum retinol. Inflammation also reduces absorption of vitamin A and increases requirement and urinary loss which together may contribute to the development of vitamin A deficiency.

Main sources of vitamin A are liver, meat, fish, cheese and butter, spinach, broccoli and mango. 90% or more of whole-body vitamin A is stored in the liver. In case of vitamin A intake below recommendation, the liver stores are sufficient to maintain functions for about 6 months.

The best measurements are the concentration of vitamin A in the liver or total body retinol.

Vitamin A deficiency is a public health problem in most developing countries due to malnutrition, especially in children and pregnant women. Clinical signs and symptoms are increased susceptibility to infections, especially of the respiratory tract, night blindness due to insufficient rhodopsin synthesis and xerophthalmia. Keratomalacia with expansion to iris and lens area leading to xerophthalmia and finally blindness is the worst complication of vitamin A deficiency.

Inflammation leads to decreased serum/plasma retinol concentration [42], [43].

Acute toxicity appear when high quantities of natural vitamin A are ingested within a few hours or days and it is manifested with increased intracranial pressure, nausea and headaches. Chronic toxicity may leads to hepatotoxic effects [44], [45]. There is no treatment of vitamin A toxicity. Retinoids (retinol, retinal, retinoic acid and related compounds) in high concentrations are teratogenic [46].

VITAMIN C

Vitamin C has numerous functions which are all based on electron donation. It is an important cofactor/ co substrate for the biosynthesis of neurotransmitters, cortisol, peptide hormones and collagen. Vitamin C can limit the inflammatory response and ischemia-reperfusion injury, improve host defense, wound healing and mood and has a role in pain reduction [47], [48], [49].

Humans are dependent on dietary intake of fruits and vegetables because they are unable to synthesize vitamin C. The DRI for vitamin C is 90-100 mg/day. Enteral nutrition should provide at least 100 mg/day and parenteral nutrition should provide 100-200 mg/day of vitamin C.

Assessment of vitamin C status can be determined from its concentration in plasma or leukocytes. Vitamin C includes L-ascorbic acid (AA) and its oxidation product dehydroascorbic acid (DHAA). Plasma vitamin C analysis is the preferred option for status assessment and serum determination should be avoided.

Normal plasma vitamin C levels are defined as >23 μmol/L. Hypovitaminosis C has been defined as plasma levels less than 23 μmol/L and vitamin C deficiency as less than 11 μmol/L [50]. Vitamin C plasma levels decline rapidly with inflammation making interpretation difficult. It may be administered oral, intramuscular, intravenous or subcutaneous. For intravenous administration the drug should be diluted with normal saline or glucose to minimize adverse reactions.

Clinical conditions with increased inflammation and oxidative stress such as sepsis, trauma, cardiac arrest, major surgery and burns are associated with high risk of depletion. In critically ill patients, low plasma vitamin C concentrations are associated with severity of oxidative stress, organ failure and mortality. Chronic depletion appears in patients after bariatric surgery, alcoholism, chronic dialysis, smoking, chronic inflammation. Clinical symptoms are lassitude, anemia, poor wound healing, myalgia and bone pain, edema, loose teeth, bulging eyes, dry hair and shortness of breath [51], [52].

Vitamin C supplementation is contraindicated in blood disorders like thalassemia, sickle cell disease and hemochromatosis. Symptomatology includes urinary calcium oxalate crystallization, renal stone formation and nephropathy, factitious hyperglycemia and hemolysis in patients with G6PD deficiency [53].

VITAMIN D (25-HYDROXIVITAMIN D)

Vitamin D is a steroid hormone precursor. Cutaneous endogenous production is possible from cholesterol with UV-B exposure, explaining the strong seasonal variations in vitamin D levels. Vitamin D supply is also possible by nutrition, but it does not cover the needs. It has several effects on many organs including bones, muscle, heart and nervous system.

The recommended daily oral intakes of vitamin D is 600-800 IU in adults and 1500-4000 IU in patients “at risk for vitamin D deficiency”. It may be administered by oral, enteral intravenous or intramuscular route [54], [55].

The valid marker for vitamin D assessment is serum/plasma concentration of total 35-hydroxyvitamin D, the sum of 25-hydroxyvitamin D3 and 25-hydroxyvitamin D2. There is no ideal time to measure the status of vitamin D.

Plasma levels of this vitamin are significantly reduced in the context of inflammation: in presence of CRP>40 mg/L, nearly all values are below reference ranges, complicating the interpretation [56].

The classic vitamin D deficiency syndrome is rickets in children and osteomalacia in adults. Vitamin D deficiency is defined by a plasma concentration of <50 nmol/L and severe deficiency by a plasma concentration <30 nmol/L. Patients at risk are those with severe kidney or liver dysfunction and chronically il patients.

Intoxication is rare, but it has been described and the symptoms include hypercalcemia, hypercalciuria, dizziness and renal failure [57].

2. VITAMIN E (ALPHA-TOCOPHEROL)

Alpha-tocopherol, the natural vitamin E with the highest biological activity is a component of all biological membranes and is the most important lipid-soluble antioxidant. It most important role is to protect membrane lipids, lipoproteins and depot fats from lipid peroxidation [58].

The DRI for vitamin E for adult men and women is 12 mg/day, 15 mg/day in pregnancy and 19 mg/day in lactation. Enteral nutrition should provide at least 15 mg/day and parenteral nutrition should provide at least 9 mg/day of alpha-tocopherol [59].

Vitamin E status is determined by the quantification of alpha-tocopherol in blood plasma or serum collected into plain, gel separator, heparin or EDTA tubes followed by HPLC coupled with ultraviolete or fluorescence detection. Plasma vitamin E is age-dependent and in children and young people significantly lower than for adults. Blood levels of vitamin C are little affected by inflammation, nevertheless the blood concentrations become less interpretable with CRP values >80 mg/L. Alpha-tocopherol is degraded in inflammatory and organ failure conditions due to increased lipid peroxidation [20.

Vitamin E deficiency is rare and it may appear in severe malnutrition. Genetic causes of vitamin E deficiency are abetalipoproteinemia with disturbance of absorption and the absence of the alpha-tocopherol transfer protein with distribution restrictions [60]. In adults with fat malabsorption, early vitamin E inadequate is generally asymptomatic. Neurological symptoms are associated with balance and coordination disorders, peripheral neuropathy and muscle weakness. In case of long-standing fat malabsorption, vitamin E supplementation improves neurological symptoms after a few months, following normalization of vitamin E status [61].

Vitamin E should be determined when there is clinical suspicion of vitamin E deficiency that include cystic fibrosis, abetalipoproteinemia and thrombotic thrombocytopenic purpura. In case of absence of clinical signs of deficiency there is no indication to measure vitamin E status.

VITAMIN K (PHYLLOQUINONE)

Vitamin K includes vitamers known as vitamin K1 (phylloquinone) and vitamin K2 (menaquinones). Vitamin K1 is produced by the plants and vitamin K2 is synthetized by human intestinal microbiota. Vitamin K includes a group of lipid-soluble molecules that possess carboxylase enzyme cofactor activity necessary for the activation of vitamin K dependent-proteins (VKDp). These include the coagulation factor proteins C, S, M, Z, factors VII, IX, X and prothrombin [62].

Main sources are leafy greens, cruciferous vegetables, asparagus, prunes and peas. Many intestinal bacteria, including E. coli synthesize vitamin K2, but no vitamin K1. Enteral nutrition should provide at least 120 µg/day and parenteral nutrition should provide 150 µg/day of vitamin K.

Fat malabsorption, malnutrition, antibiotic and anticoagulant treatments are the most common causes of vitamin K deficiency. Vitamin K can contribute to significant

bleeding, poor bone development, osteoporosis and increased cardiovascular disease. Clinically significant bleeding has mainly been reported in newborns and extremely inadequate intake or malabsorption syndromes.

Vitamin K1 and K2 are not associated with toxicity. Rare anaphylactoid reactions with bronchospasm and cardiac arrest after intravenous vitamin K1 administrated for anticoagulation reversal have been reported [63]. The synthetic vitamin K3 is very toxic and could cause jaundice, hyperbilirubinemia, hemolytic anemia and kernictus in infants.

Vitamin K status should be determined by a combination of biomarkers with dietary intake, as there is no agreed standard.

Author Contributions:

V.M.M. conceived the original draft preparation. V.M.M., R.I.D., A.I.N. and L.B.G. were responsible for conception and design of the review. V.M.M., L.B.G., A.I.N. and R.I.D. were responsible for the data acquisition. V.M.M. was responsible for the collection and assembly of the article/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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