**Review article**

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# HYDROSOLUBLE HYPERVITAMINOSIS: ETIOPATHOGENESIS OF WATER-SOLUBLE VITAMIN OVERDOSE

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Water-soluble vitamins, vitamin C and vitamin B complex, are traditionally considered safe due to a lack of substantial evidence of their toxicity. Nevertheless, given the growing availability and widespread use of vitamin supplements, new evidence and reports of hypervitaminosis and toxicity related to excessive consumption of water-soluble vitamins are increasing. The current assessment of safe levels of vitamin intake should be conducted in the context of fortified foods, food supplements, and other nutrients. There is a wide spectrum of overdose-related signs and symptoms, including most commonly nausea, vomiting, diarrhea, headache, fatigue, skin changes, hypersensitivity, neurological events, liver dysfunction, nephrolithiasis, etc. There are also concerns about certain findings on the association of vitamins with cancerogenesis, pregnancy complications, and neurodevelopment. Most people do not need to supplement with water-soluble vitamins when on an adequate and varied diet. Otherwise, experts recommend consulting a medical professional to reduce the likelihood of adverse effects from vitamin supplements.

**Key words**: ascorbic acid, vitamin B complex, niacinamide, folic acid, dietary supplements

Pregledni rad

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# HIDROSOLUBILNA HIPERVITAMINOZA: ETIOPATOGENEZA PREDOZIRANJA VITAMINIMA RASTVORLJIVIM U VODI

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Vitamini rastvorljivi u vodi, vitamin C i kompleks vitamina B, tradicionalno se smatraju bezbednim zbog nedostatka značajnih dokaza o njihovoj toksičnosti. Ipak, s obzirom na sve veću dostupnost i široku upotrebu vitaminskih suplemenata, sve je više dokaza i izveštaja o hipervitaminozi i toksičnosti povezanim sa prekomernom upotrebom vitamina. Trenutna procena bezbednih nivoa unosa navedenih vitamina treba da se vrši u kontekstu obogaćenih prehrambenih proizvoda, dodataka ishrani i drugih nutrijenata. Postoji širok spektar znakova i simptoma povezanih sa predoziranjem, uključujući najčešće mučninu, povraćanje, dijareju, glavobolju, umor, promene na koži, preosetljivost, neurološke događaje, disfunkciju jetre, nefrolitijazu itd. Takođe postoji zabrinutost zbog određenih nalaza o povezanosti vitamina sa kancerogenezom, komplikacijama u trudnoći i razvojem nervnog sistema. Većini ljudi na adekvatnoj i raznovrsnoj ishrani nije potrebno da uzimaju suplemente hidrosolubilnih vitamina. U suprotnom, stručnjaci preporučuju konsultacije sa lekarom, što može ograničiti verovatnoću neželjenih efekata od konzumiranja vitaminskih suplemenata.

**Ključne reči**: askorbinska kiselina, kompleks B vitamina, niacinamid, folna kiselina, dijetetski suplementi

## Introduction

Vitamins are essential substances needed for a wide variety of metabolic functions. They act as prosthetic groups or cofactors of enzymes and are required in small amounts; however, they are usually necessary to take daily. Vitamins are found in natural sources as well as pharmacological compounds. Due to the body's ability to store liposoluble (fat-soluble) vitamins (A, D, E, and K) in adipose tissue and the liver, and to a lesser extent, eliminate them, higher intake of these vitamins may cause toxicity. On the other hand, it is generally accepted that water-soluble (hydrosoluble) vitamins (C and B complex) are non-toxic (1-4).

The US Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI) did not establish tolerable upper intake levels (UL) for water-soluble vitamins because of a lack of evidence of their toxicity. Data was inadequate for quantitative risk assessment, which makes it difficult to establish a UL. Moreover, new DRIs have not been updated since 1998 because current scientific data does not justify changing the existing standards. There is a lack of new research indicating a need for revision, as well as low priority due to insufficient evidence to start comprehensive research (5).

However, the European Food Safety Authority (EFSA) Panel on Nutrition, Novel Foods and Food Allergens (NDA) (6-8) and several other European medical societies (9-11) keep monitoring the safety of vitamin consumption, among others, and deliver a scientific opinion on dietary reference values and intake levels more frequently. Their assessment of maximum vitamin levels is done in the context of fortified food products, food supplements, and other nutrients, with the highest level of intake given on reasonable confidence in the absence of adverse effects (6-11).

The long-standing assumption that water-soluble vitamins are safe at any intake may be changing, as reports of hypervitaminosis and toxicity related to excessive consumption are increasing (1, 12-16). The crucial reason for this change is the growing availability and widespread use of water-soluble vitamin supplements. The benefits of vitamins are widely advertised, and the need for daily intake is emphasized. Vitamins are sold in many different formulations as food supplements and as fortification in various foods. They are sold in various combinations and dosages, and in accordance with the different needs of children, males, females, pregnancy, and the elderly. Multivitamin supplements are often recommended to enhance athletic performance, weight control, improve immune function, and prevent chronic diseases. Sometimes they are combined with botanical ingredients, trace elements, and

probiotics. Rarer reasons for excessive vitamin intake include accidental ingestion or iatrogenic causes (1, 17, 18).

According to the National Health and Nutrition Examination Survey (NHANES) on dietary supplement use, multivitamin/mineral supplements were the most commonly consumed supplements in the United States from 2017–2018. These products include three or more vitamins and at least one mineral. Females were more likely to take multivitamin/mineral supplements than men, as were older adults, children of mothers who take supplements, people with higher education, and lower body mass index (BMI) (18).

Manifestations of water-soluble vitamin hypervitaminosis may be very diverse. Some of the most common include nausea, vomiting, indigestion, headache, fatigue, drowsiness, skin changes, hypersensitivity, neurological events, liver dysfunction, etc. The toxic symptoms arise due to exaggerated and prolonged physiological and biochemical actions of the vitamins (1, 12-16).

This study aimed to summarize current knowledge about hypervitaminoses of water-soluble vitamins, adverse effects when used therapeutically, with special attention to their pathogenesis and clinical manifestations.

**Methods**

We assessed all available literature regarding the adverse effects and toxicity of water-soluble vitamins by searching the reliable PubMed and Scopus databases until February 2026. Studies that examined the vitamins' effects in experimental (*in vitro*) environments, animal models, and human studies were all acceptable. Also, the articles' references were reviewed for relevant publications.

**Vitamin B complex hypervitaminosis**

Vitamin B-complex comprises vitamins involved in enzymatic reactions related to energetic metabolism, regulation of DNA replication, transcription, and protein translation. They participate in many redox reactions and are part of the antioxidant system. Therefore, these vitamins affect a range of organic systems, including the cardiovascular, immune, endocrine, musculoskeletal, and nervous systems. Daily supplementation with B-complex was even found to reduce the risk of cognitive impairment and Alzheimer's disease. More precisely, intake of vitamins B6, B9, and B12 was linked to reduced hypermethylation of redox-related genes, which may contribute to better cognitive reserve (1, 12).

The high prevalence of supplemental vitamin B use warrants investigation of its influence and associations with health risks. Scientific investigations report that B-complex hypervitaminosis can be

associated with disturbed carbohydrate metabolism, alterations in skin and mucous membranes, fatty liver, hypersensitivity, problems with nerve transmission and myelination, neuroendocrine regulation, carcinogenesis, and many other health problems (1, 13-16).

**Vitamin B1 (Thiamine)**

Thiamin is involved in energetic metabolism, cellular synthetic processes, neurotransmitter biosynthesis, etc. There is no upper limit for intake for this vitamin, because most of the excess is eliminated by the urine. Scientific Committee on Food (SCF) found no lowest-observed-adverse-effect level (LOAEL) nor no-observed-adverse-effect level (NOAEL) for thiamine in 2001. In 2016, the European Food Safety Authority (6) published population reference intake values for thiamine, recommending intakes of 0.4 mg per 1,000 kcal for all age, gender, and special life situations groups (e.g., pregnancy and lactation). According to physical activity levels calculations, this corresponds to between 0.56 and 1.24 mg per day (5, 6, 9).

Vitamin B1 deficiency is a well-known cause of a specific disease, historically termed as beri-beri. In current-day practice, it is commonly related to alcoholism, and therefore, it is not an uncommon condition. It requires immediate parenteral thiamine replenishment. Thiamin deficiency is a general hypoenergetic state producing cardiovascular, muscular, neurologic abnormalities, and mental changes. The so-called dry beriberi may progress to the development of Wernicke encephalopathy, Korsakoff psychosis, and mixed sensory and motor neuropathy (1, 13, 14, 19). Wernicke encephalopathy is an acute emergency, where an urgent thiamine replacement is necessary to avoid progression and irreversible brain damage. Besides alcohol dependency, certain populations are more susceptible to vitamin B1 deficiency, including malnourished patients, patients following bariatric surgery, patients with gastrointestinal diseases, pregnancy complications, hyperthyroidism, malignancies, renal failure, chronic diuretic therapy, etc (13, 14, 20, 21).

On the other hand, cases of hypervitaminosis are scarce. Nevertheless, there is evidence that a synthetic thiamin form, thiamine hydrochloride, used in treating deficiency, can be associated with adverse effects, including nausea, allergic reactions, urticaria, digestive distress, and other side effects (14).

Thiamine hydrochloride injection is specifically approved and indicated for use when administering intravenous (IV) dextrose to individuals with marginal thiamine status (19). Parenteral thiamine treatment is considered to have a very high safety profile. However, there is a lack of consensus on the

appropriate treatment of Wernicke encephalopathy, specifically, thiamine dosage, protocols, and prescribing patterns (13, 22, 23).

Several studies and case reports show allergic reactions upon thiamine treatment (14, 23). A study from 2019 concluded that the risk of anaphylaxis is low and the risk-benefit ratio is favourable given the severity of potential brain damage, although it was difficult to estimate the incidence because the number of doses given was unknown (23). Over half of the adverse reactions to IV preparation (Pabrinex), summarized as serious adverse reactions, involved the immune system, nervous system, and skin and subcutaneous tissue. Sneezing and mild asthma are reported to be early signs of developing an allergic reaction (23). Anaphylactic or anaphylactoid reactions are reported following IV administration (13).

There are scarce reports of vitamin B1 overdose or adverse reactions from oral preparations and supplements. Osman et al. (24) described a case of angioneurotic oedema secondary to oral thiamine hydrochloride (200 mg) treatment in a female patient with alcohol dependency syndrome. Patient developed sudden onset bilateral lower limb swelling with erythema that subsided in 4 days following thiamine discontinuation.

A review of mitochondrial medicine therapies shows that thiamine supplementation therapy for a very rare genetic condition, thiamine pyrophosphokinase (TPK) deficiency, can cause nausea when doses are above 7.000 mg daily, although the recommendation in this case is 20 mg/kg/d (max: 900 mg/d) (25). Reportedly, a thiamin overdose can be related to paralysis, ataxia, restlessness, convulsions, and heart and lung dysfunction (1, 14, 26). However, reliable scientific evidence is lacking.

**Vitamin B3 (Niacin)**

Vitamin B3 or nicotinic acid (niacin) and nicotinamide (niacinamide) form two important coenzymes: nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). These represent pivotal elements in energetic crossroads and are needed for basic synthetic processes in cells. The minimum intake of niacin is 20 mg/day, while therapeutic doses go up to 3 g/day (27).

Niacin has been used for a long time in patients with hyperlipidemias, alone or in combination with statins, and provides efficient and safe reduction in lipid levels associated with atherosclerosis. Its effects include increasing the high-density lipoprotein cholesterol (HDL-C) level while decreasing the levels of low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein (VLDL), triglycerides, and Lp(a) (28, 29). Through its receptor on adipocytes, hydroxy-carboxylic-acid-receptor 2, niacin reduces

triglyceride lipolysis and release of free fatty acids. This is considered only a part of its antilipemic actions and is transient. Niacin also directly affects several hepatic enzymes involved in apolipoprotein degradation, secretion, and receptors. For instance, it accelerates hepatic apolipoprotein B degradation. Besides the antilipemic effects, niacin's antiatherogenic properties are supposed to occur through mechanisms involving its receptors on immune cells and endothelium. Altogether, niacin treatment of hyperlipidemia is associated with significant reductions in cardiovascular morbidity (28-30).

One of the well-established side effects of niacin treatment is the niacin-induced flushing syndrome. It is a common non-allergenic response in patients with long-term niacin treatment. It is a rapid, dose-dependent, but transient response that diminishes with time. The pathophysiological effects rely on the stimulation of the niacin receptor on dermal Langerhans cells and keratinocytes that are consequently activated to produce prostaglandins (i.e., PGD2, PGE2) via cyclooxygenase 1 (COX1) and COX2, respectively. Prostaglandins further act on capillaries and cause vasodilatation in the skin, with accompanying itching, redness, and warmth. The response diminishes within a week due to a gradual decline in PGD2 secretion with repeated niacin use. Because of the discomfort it produces, compliance with the niacin treatment might be compromised. Therefore, niacin extended release (NER) formulations, which produce fewer episodes of flushing, are produced (28, 31).

Several additional disturbances have been reported when high doses of niacin are used. These include liver dysfunction, a tendency to develop fasting hyperglycemia and hyperuricemia with possible progression to gout, gastrointestinal tract (GIT) disturbances, and acanthosis nigricans (1, 15, 32).

Niacin can induce or aggravate gout because it raises the uric acid levels in the blood. This is because it inhibits uricase, the oxidase that converts uric acid into a more soluble compound and additionally changes the degree of uric acid excretion. Diminished excretion is supposed to be due to tubular changes induced by ketoacids or nicotinic acid metabolites (15, 32). Continuous exposure to nicotinic acid causes alterations in carbohydrate metabolism. The hyperglycemic effects are observed in patients with diabetes mellitus, but the glucose increase is of modest severity and usually transient. Nevertheless, avoidance of niacin use in these patients is advised (15). Unlike the transient decline in free fatty acid levels during short-term niacin use (of a few hours), its prolonged use leads to increased release and levels of free fatty acids, the so-called rebound increase in free fatty acid levels. These derangements represent the background to the development of insulin resistance (reduced insulin sensitivity) and hyperglycemia. It is determined that the induction of insulin resistance in chronic niacin exposure relies

on a greater availability of circulating fatty acids to muscle tissue and fat oxidation, but not intramyocellular lipid content (15, 33, 34).

Additionally, sustained-release niacin forms, particularly supplemental forms, have been associated with hepatotoxicity (15, 32). The side effect is reflected in a moderate increase in the serum aminotransferase levels, jaundice, and GIT symptoms. The symptoms commonly arise with a niacin dose of above 3 g/day and may resolve spontaneously. One suggestion is that hepatotoxicity is mediated by niacin metabolites (35). Alterations in the NAD/NADH ratio with increased redox potential are associated with inhibition of fatty acid oxidation and fat accumulation in hepatocytes. In addition, niacin affects liver synthetic machinery and results in decreased protein synthesis, a decline in serum albumin, and impairment of coagulation (34, 36, 37).

Last but not least, niacin supplementation divided the opinions over its use in endurance athletes. Some studies have shown that niacin supplementation may lead to a decrease in overall endurance performance. Excessive niacin amounts might impede fat metabolism by blocking the release of free fatty acids, which provide energy during prolonged exercise (38).

**Vitamin B6 (Pyridoxine)**

Vitamin B6 or pyridoxine has two active coenzyme forms: pyridoxal 5' phosphate (PLP) and pyridoxamine 5' phosphate (PMP). Vitamin B6 is involved in a wide variety of functions in the body, including processes of protein and amino acid metabolism, the metabolism of one-carbon units, carbohydrates, lipids, gluconeogenesis, and glycogenolysis, the biosynthesis of neurotransmitters, hemoglobin formation, immunomodulatory functions, etc. Vitamin B6 deficiencies are relatively rare. Malabsorption syndromes, alcoholism, end-stage kidney disease and receiving dialysis, chronic inflammatory rheumatic diseases, preeclampsia, and eclampsia are some of the conditions associated with a risk of having B6 deficiency. Vitamin B6 is usually available in various multivitamins in the form of pyridoxine hydrochloride, which is also a treatment for pyridoxine deficiency (a licensed medicine). Pyridoxine is proposed to alleviate the symptoms of premenstrual syndrome, carpal tunnel syndrome, neuropathies, and even autism and hyperkinesis (1, 10, 39-41). High-dose pyridoxine supplementation is reported by athletes, such as bodybuilders, possibly due to a higher meat intake (42). Recommended pyridoxine hydrochloride maximum daily doses range between 0.5 and 30 mg, while the pyridoxine maximum daily dose is set at 10 mg. Large doses of vitamin B6 are quickly eliminated in the urine (1, 10, 39, 40).

In 2006, EFSA lowered the advised safe upper level of vitamin B6 from 100 mg/day to 25 mg/day, because of an increasing number of cases with neuropathies. Subsequently, in 2023, data were re-evaluated based on new data, and the upper limit for vitamin B6 was updated to 12 mg/day for adults (3, 41, 43, 44).

Hypervitaminosis is considered very rare and is thought to result from long-term excessive use of supplements. Excessive vitamin B6 intakes are established risk for developing peripheral axonal polyneuropathy. Both sensory and motor pyridoxine-associated polyneuropathies are demonstrated (10, 40, 45, 46). Mostly, it manifests as sensory-predominant polyneuropathy affecting both large and small fibres. It is observed that peripheral nerve hyperexcitability precedes small fiber dysfunction by months. Small-fiber neuropathies may remain underdiagnosed, as they are more challenging to diagnose (43, 47-49).

Prolonged use of high doses daily (300-600 mg/day) is reported to cause severe progressive sensory neuropathy with sensory ataxia, paresthesia, photosensitivity, nausea, dizziness, a loss of deep tendon reflexes, etc (1, 26, 44, 45, 50). Kulkantrakorn et al. (45) describe three patients with pyridoxine-induced sensory ataxic neuropathy (in their 80s) who took 600 mg of pyridoxine each day for 3-10 years, in the form of vitamins B combination tablet. Electrodiagnostic tests showed symmetric axonal sensorimotor polyneuropathy, without significant improvement after vitamin discontinuation. The symptoms of vitamin B6 overdose usually resolve upon discontinuation unless irreversible damage has occurred (26).

Moreover, the safety of vitamin B6 should be taken into account in patients with kidney failure. An animal study provides evidence of a 5- to 10-fold increase in susceptibility to pyridoxine-induced neuronopathy in anephric rats (51).

Krishnan et al. (47) describe a man with pyridoxine-induced generalized fasciculations, mimicking the early features of amyotrophic lateral sclerosis. Presenting with eight-month-evolving muscle twitching, the patient developed undulating movements and twitching while asleep, allodynia and hyperesthesia, a burning sensation over the soles, and widespread intermittent paresthesia. After thorough examinations and a disease exclusion process, it was concluded that vitamin supplementation is the cause of his symptoms. He was taking vitamin supplements, containing a total B6 amount of 95 mg daily, which resulted in serum levels of 1179 nmol/ml (normal range 35–110 nmol/ml). Fasciculations

resolved after cessation of vitamin intake, but were followed by the development of dermatitis patches and desquamation involving his feet, likely as a coasting effect of a drug withdrawal.

Autonomic symptoms of polyneuropathy have also been reported. A case presented a 41-year-old female with severe pyridoxine toxicity causing 2 years of progressive sensory polyneuropathy. This was accompanied by autonomic nerve fiber damage, revealed by abnormal responses to quantitative sweat testing and cardiovagal function testing (48).

Several pathogenic mechanisms have been proposed to explain pyridoxine-related neuropathy and the preferential injury of sensory neurons. One of them is a disruption of γ-aminobutyric acid (GABA) neurotransmission in peripheral nervous tissue, resulting in excitotoxicity and neurodegeneration. Based on knowledge of hereditary pyridoxal kinase (PDXK) deficiency, characterized by axonal sensory neuropathy, a study proposes that high serum vitamin B6 concentrations may result in similar conditions by inhibiting PDXK. Decreased PDXK activity reduces GABA synthesis, whereas pyridoxine's inability to cross the blood-brain barrier confines PDXK inhibition to peripheral tissues. Therefore, disrupted GABA signaling may lead to the development of peripheral sensory neuropathy (47, 49).

Another mechanism suggests pyridoxine-induced cytotoxicity via competitive inhibition of the active form of the vitamin, PLP, resulting in its functional deficiency. This is known as the pyridoxine paradox (43, 47). Accumulation of free pyridoxine after chronic supplement use is considered responsible for such action, as specific vitamers (forms of a vitamin) did not show the same (43). In an in vitro study, inactive pyridoxine could inhibit PLP-dependent enzymes. Unlike other B6 vitamers, pyridoxine produced cytotoxic effects on cultured neuronal cells, while in animal studies it induced neuronal damage after intraperitoneal injection (43, 51). The studies emphasize that, besides dosage, an important determinant in the development of neuropathy is a vitamer present in the supplement, as well as inter-individual differences in vitamin B6 pharmacokinetics and sensitivity to toxicity (43, 44). Susceptibility might depend on the intrinsic variability in the vitamin intestinal absorption, as well as kidney function (47, 49). Additionally, daily pyridoxine use for a prolonged period seems to alter the rate of pyridoxine excretion by decreasing its clearance (43, 49, 50).

A definitive threshold for neuronal injury is currently unclear, as reports show the occurrence of neuropathies at different dosages of vitamin B6 intake. Neuropathic complaints were associated with vitamin B6 dosing range 0.5 mg – 250 mg daily and with different plasma levels of PLP (42, 44). There

are cases describing neuropathic symptoms in those taking pyridoxine even below the recommended EFSA upper limit (41, 43, 49).

EFSA proposed the same upper limit of vitamin B6 (12 mg/day) for pregnant and lactating females as for general adults (lower for infants and children). Nevertheless, higher doses are sometimes prescribed to treat nausea and vomiting of pregnancy during the first trimester. Comparably, cases of neuropathy were observed in this group with large doses, but it seems there is no increased risk for major malformations and other adverse effects (52).

A study observed an increase in vitamin B6 overdoses in bariatric surgery patients (46). Their condition necessitates lifelong surveillance for nutrient deficiencies, hence the recommended vitamin supplementation. Although vitamin B6 is not among the recommended vitamins, it is present in most of the multivitamin products, leading easily to overdose. The study shows the number of overdoses reached close to 40% of dosages in 8-year-studied period. Therefore, the need for precautions and a definition of clear guidelines for vitamin B6 supplementation (46).

Pyridoxin toxicity also encompasses dermatitis, a painful skin rash with patches and desquamation. It is suggested to be related to a phototoxic reaction to an agent (1, 26, 47).

Last but not least, some investigations correlated vitamin B6 use with an increased cancer risk. In contrast to females, vitamin B6 use of over 20 mg/day was associated with a 30% to 40% increase in lung cancer risk among men, compared with nonusers. The risk was higher in males who smoked (16). On the other hand, there are investigations opposing associations of the vitamin B group with cancers, such as a meta-analysis by Zhang et al. Their analysis included 18 randomized controlled trials, reporting the data on 74,498 individuals, which led to the conclusion that vitamin B supplementation does not have an effect on cancer incidence or total mortality (2).

**Vitamin B9 (Folate)**

Folate is the natural form of vitamin B9 found in foods, while folic acid is the synthetic, more stable form used in supplements. Natural folates are in the tetrahydrofolate (THF) form and usually have additional glutamate residues. The active monoglutamyl form, 5-MTHF (or L-methylfolate) can also be found in supplements. Folate functions as a coenzyme in single-carbon transfers. It is a part of the one-carbon metabolism pathway, a set of reactions involved in basic cellular processes (3, 53-55). Vitamin B9 is essential for the proper production of nucleotides, DNA synthesis, DNA methylation, and cell division. It prevents neural tube defects in fetal development and supports cardiovascular health by breaking down

homocysteine. It participates in the conversion of homocysteine to methionine in the synthesis of S-adenosyl-methionine. Folate deficiency can lead to the development of macrocytic anemia, and vitamin B9 supplements are used for treating this kind of deficiency-related anemia (53, 54, 56, 57). People with malabsorptive disorders may have folate deficiency. It is estimated that approximately 20%–60% of patients with inflammatory bowel disease have folate deficiency (54, 58). In this regard, food fortification with synthetic folic acid has become a mandatory public health strategy in over 80 countries, primarily designed to prevent neural tube defects (59).

Based on the average daily intake sufficient to meet nutrient requirements, RDAs are recommended as dietary folate equivalents (DFE), which account for the different bioavailability of folate (50%) and folic acid (85%) from food. Adult needs are defined as 400 µg DFE, while pregnancy requires a higher intake of 600 µg DFE (5, 54, 57). Individual folate status can be assessed by measuring serum folate concentrations (adequate above 3 ng/ml), which are sensitive to recent dietary intake, and by erythrocyte folate concentrations (140 ng/ml), which provide a longer-term measure of folate intakes (54, 56, 60).

Several side effects of high intake of vitamin B9 are reported. An excessive intake of synthetic vitamin B9 supplements presumes taking over 1000 µg/day, and this was set as the safe upper level of intake by the Food and Drug Administration (54). Listed symptoms of hypervitaminosis B9 include gastrointestinal problems, anorexia, nausea, seizures, insomnia, liver dysfunction, allergic reactions, immune dysfunction, etc (1, 26, 54, 61). Receiving high-dose folate supplements as a therapy may mask vitamin B12 deficiency and its neurological consequences (54, 57, 62). In addition, disruption of the one-carbon metabolism is considered to promote carcinogenesis, although the conclusions about the role of folate in this process are inconsistent (3, 55, 59, 63, 64).

High intake of folic acid is associated with a rise in unmetabolized folic acid (UFA) blood concentrations due to the overwhelmed reaction of its conversion to 5-MTHF. Evidence suggests that this can be a result of low and variable dihydrofolate reductase (DHFR) activity in intestinal mucosa and/or the inhibitory effect of folic acid on DHFR (65, 66). Smaller amounts of folic acid, consumed more frequently, produce higher UFA compared to the same total dose consumed at once (67). Individuals with the methylenetetrahydrofolate reductase (MTHFR) C677T gene polymorphism have a reduced ability to process folic acid, leading to the accumulation of UFA. It is advised that these individuals use 5-MTHF or 5-formyl-tetrahydrofolate (5-FTHF) supplements in place of folic acid, as these can mitigate harmful

accumulation of UFA (57). It is considered that the negative consequences of UFA are related to impairment of the one-carbon metabolism, DNA methylation, and replication. Inhibition of cobalamin-dependent methionine synthase is also reported, which in turn, induces accumulation of unmetabolized homocysteine and oxidative stress (68-70).

Unmetabolized folic acid was associated with several adverse effects on health, such as cognitive performance in persons who are vitamin B12-deficient. Here, high UFA levels were associated with lower cognitive test scores, whereas persons in a subgroup with higher serum 5-MTHF and normal vitamin B12 levels achieved higher cognitive test scores. Concentrations of 5-MTHF were inversely related to macrocytosis, independent of circulating UFA. Damage to the nervous tissue was likely to arise from the combination of decreased methionine synthase activity, due to low vitamin B12, and simultaneously increased folic acid intake. Currently, there are no definitive conclusions about health effects from exposure to UFA (59, 71).

Unmetabolized folic acid has been associated with reduced natural killer (NK) cell count and cytotoxic activity. There was an inverse correlation between plasma UFA concentration and NK cytotoxicity in a study of postmenopausal females (61). An animal study showed that reduced NK cell cytotoxicity due to high folic acid was partially related to reduced production of IL-10. LPS-stimulated splenocytes from mice on a high folic acid diet produced less IL-10 (72). Also, a study from 2017 confirmed that 90-days daily dose of 5 mg is associated with increased levels of UFA and reduced NK cell cytotoxicity (73).

Dietary folate deficiency but also folic acid supplementation both impair folate-dependent biosynthetic processes in lymphocytes, impair production of lymphocytes, and compromise hematopoiesis. Both low and excessive levels of folic acid similarly impacted global DNA methylation, DNA damage induced by oxidative stress, and DNA base excision repair gene expression, in a human lymphoblastoid cell line (LCL) (65, 74). It is reported that excess folic acid could mimic folate depletion in LCL. Findings support a standing that high consumption of folic acid can precipitate genomic instability in peripheral lymphocytes (75). Animal study by Henry et al. (74) showed significant defects manifesting in the B-progenitor compartment. They primarily observed proliferative defects of isolated B-progenitors due to deficiencies in the nucleotide synthesis pathways, from mice fed with both folate-deficient and supra-folate diets. Also, hematopoietic progenitors were deficient in their ability to reconstitute hematopoiesis post-irradiation.

Pregnant females and those planning pregnancy are advised to increase their daily vitamin intake with at least 400 µg of folic acid to lower the risk of birth defects. However, UFA might be associated with certain adverse pregnancy outcomes, especially in mothers carrying the C677T polymorphism (57). Findings on vitamin B9 supplementation in pregnancy vary widely, and depending on the country and population. A recent study with a European female group highlighted that pregnant females are "not particularly adherent to recommendations" of folic acid supplementation (76). Unlike this, investigations from the USA and Canada show better compliance. More than half of the females reported some form of folic acid intake before and during pregnancy in a study from North Carolina. Ten percent took doses that exceeded the upper limit, and Caucasians and those with higher education were more likely to report high intake (77). The majority of the Canadian pregnancy cohort took supplements containing 1000 µg folic acid, resulting in exceeding the upper recommended level (78).

One of the potential adverse effects of excessive folic acid use in pregnancy is a higher risk of autism spectrum disorders (ASD). A study by Raghavan et al. (79), which included 1257 mother-child pairs, demonstrates a 'U-shaped' relationship between maternal multivitamin supplementation frequency and ASD risk. That is, maternal multivitamin self-reported supplement intake ≤ 2 times/week and > 5 times/week demonstrated statistically significantly increased risk for ASD. Very high levels of maternal plasma folate at birth (≥ 60.3 nmol/L) had a 2.5 times increased risk of ASD, as well as very high vitamin B12 (≥536.8 pmol/L) levels, with the same 2.5 times increased risk. The findings suggest a possible perturbation in one-carbon metabolism, which can have an impact on brain development. Animal model studies observed several pathogenic mechanisms regarding these vitamins. Increased maternal folate during gestation changed gene expression patterns in cerebral and cerebellar hemispheres, including those related to GABA and dopamine-serotonin pathways and synaptic plasticity (69, 70, 79).

Maternal oversupplementation with folic acid has also been connected to birth defects like cleft lip (80), poor psychomotor development (81), insulin resistance (82), gestational diabetes mellitus (83), and a questionable role of folic acid in the development of an early childhood allergic disease (84, 85).

Folate supplements might reduce serum levels of commonly used antiepileptic medications, such as phenytoin, carbamazepine, and valproate. Conversely, antiepileptic drug treatment is found to reduce folate levels and is associated with a risk for hyperhomocysteinemia (54, 86). Although historically viewed as a pro-epileptogenic agent, current research advocates that folic acid, in standard, non-

supraphysiologic concentrations, does not promote seizures in most patients. Also, folic acid supplementation is essential for females of childbearing potential with epilepsy, given that antiepileptic medications can reduce folate levels (86-88). There is one more specificity: high-dose folic acid supplementation (>1 mg daily) of mothers during pregnancy was found to be associated with 20% increased overall cancer risk, with a consistent association with non-Hodgkin lymphoma. The high-dose supplementation has also been linked to increased cancer risk in children born to mothers with epilepsy (64, 89).

**Vitamin B12 (Cobalamine)**

Metabolically active forms of vitamin B12 are methylcobalamin and 5-deoxyadenosylcobalamin. As a cofactor of methionine synthase, it participates in the conversion of homocysteine to methionine and in the production of S-adenosylmethionine, a universal methyl donor. As a part of the enzyme methylmalonyl-CoA mutase, it is involved in the metabolism of propionate, a short-chain fatty acid (90, 91). Cyanocobalamin and hydroxycobalamin are administered parenterally as prescription medications for the treatment of vitamin B12 deficiency. Inadequate vitamin B12 amount is more likely to occur in the elderly, vegetarians, patients with pernicious anemia, gastrointestinal disorders (e.g., *Helicobacter pylori* infection), or gastrointestinal surgery (90, 91).

The US Standing Committee on the Scientific Evaluation of DRI did not establish a tolerable upper intake level because vitamin B12 is generally considered to be safe. Even at high therapeutic doses, it is considered safe (5). European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition, and Allergies set an adequate intake for cobalamin at 4 µg/day for adults, considering data on biomarkers of cobalamin status and observed intakes in several EU countries. Notably, information was limited on the dose–response relationships between cobalamin intake and biomarkers (7, 11). Nevertheless, some reports describe cases of elevated serum vitamin B12 levels (hypercobalaminemia), overdose, and certain adverse effects related to therapeutic administration. Studies report the occurrence of allergic reactions, fatigue, anxiety, insomnia, paresthesia (tingling and numbness), alterations in vascular reflexes, palpitation, and even heart failure, but the evidence is based mostly on case reports (1, 26). Mechanisms found to increase serum vitamin B12 levels include excessive intake (oral or parenteral), liberation from internal reservoirs (e.g., the liver, myeloid lineage), and an increase in transcobalamin or reduced clearance (92-94).

Hypercobalanemia can result from certain conditions, including renal failure or liver diseases, myeloproliferative disease, solid tumors, and infections (95-98). One of the mechanisms described leading to hypercobalanemia involves the production of circulating autoantibodies to transcobalamin II, which result in retention of both transcobalamin II and vitamin B12 due to impaired clearance. Hypercobalaminemia is strongly associated with myeloproliferative neoplasms. Elevated vitamin B12 levels are believed to arise from increased transcobalamin I secretion by proliferating leukocytes (94). Additionally, patients diagnosed with scrub typhus infection had significantly higher mean serum transcobalamin II levels than normal, presumably due to the reticuloendothelial system stimulation (95-98).

Hypercobalaminemia might be more frequent than thought, and very high levels should be considered a warning sign of serious underlying conditions, such as malignancies. Also, functional vitamin B12 deficiency, due to qualitative abnormalities of transcobalamin and their receptors, may be linked to signs of deficiency at any serum level (92). Besides, analytical interference can present as persistently high vitamin B12 lab values, such as with the formation of cobalamin macrocomplexes. The absence of any symptoms, discomfort, or other lab anomalies should direct the search toward the lab measurement technique (99). The cause of supra-physiological cobalamin plasma levels is sometimes due to immune complexes of vitamin B12 and IgG antibodies, which are biologically inactive (97).

There are several case reports that highlight the association of vitamin B12 and neurological issues. A case from 2024 describes the correlation of significantly elevated serum B12 levels (over 2,000 pg/mL) and paresthesia. A 49-year-old female patient with a history of Hashimoto's thyroiditis and irritable bowel syndrome complained about an extensive "random" paresthesia in limbs and upper back, muscle spasms, and sharp pain. There was no evidence from the images and nerve conduction studies to explain the patient's symptoms. Her medication list included 500 mcg cyanocobalamin and 20 mcg vitamin B12 from multivitamin supplementation (216% over the RDA). Discontinuation of vitamin B12 improved her symptoms, while the high blood B12 levels decreased (93). Another case describes the skin and CNS toxicity as a result of repeated, high doses of cyanocobalamin in a 24-year-old female with multiple autoimmune conditions, severe pernicious anemia, psoriasis, and mild thyroid goiter related to Hashimoto's thyroiditis. She was treated with multiple daily doses of 1 mg of cyanocobalamin. After several weeks, the patient noticed acneiform eruptions on the face, neck, chest, and back, and suffered palpitations, anxiety, akathisia, headache, and insomnia. A serum B12 level of 1858 pg/mL was

reported. After stopping the treatment, all symptoms disappeared in the following weeks (100). The proposed mechanism behind the acneiform eruptions considers cobalamin-induced modulation of the metabolic activities of Propionibacterium acnes in the skin (101).

A case of mixed-state bipolar disorder following vitamin B12 overdose was recently published. A 48-year-old female patient presented with persistent symptoms, including insomnia, akathisia, tics, restlessness, depressed mood, etc. She was self-administering 1 mg of cyanocobalamin intramuscularly daily without a clear reason, although the physician was aware of it. The authors argue that the overdose may have acted as an environmental trigger leading to the onset of bipolar disorder, likely based on epigenetic mechanisms altering the gene expression pattern (102).

An interesting case reported a 76-year-old male with hypercobalaminemia induced by oral intake of an energy drink after total gastrectomy. Vitamin B12 level increased up to 36-fold higher than the normal range, presumably because the patient consumed half a bottle of an energy drink each day. In this case, the patient did not show any symptoms or laboratory abnormalities related to high vitamin B12 levels (95). Several other reports demonstrated relationships between elevated serum vitamin B12 levels and multivitamin use in patients with total gastrectomy (103, 104). The reports underline the importance of considering energy drinks as potential sources of excessive vitamin or mineral intake, especially given the ongoing increase in annual consumption.

The intake of vitamin B12 was significantly associated with glaucoma development in a study that investigated 594 cases from the NHANES 2005-2008 database. The given explanation for pathophysiology encompasses two mechanisms. Presumably, cobalt is the main cause of visual impairment, optical neuropathy, and retinopathy. Another mechanism involves a functional deficit of vitamin B12 despite the high plasma values, leading to increased homocysteine levels, neuropathy, and a risk factor for glaucoma development (105).

As mentioned in the part about vitamin B9, both vitamins are found to be related to the risk of ASD occurrence, that is, very high as well as deficient levels. The risk is reflected in changes in gene expression (DNA methylation), such as those for neurotransmitters and synaptogenesis, and for vitamin B12, the processes of myelination, cellular differentiation, and signaling (70, 79, 106).

Some evidence links higher vitamin B12 intakes or blood concentrations with increased risk of cancer, although other studies contradict those findings (16, 107-109). Arendt et al. show, in a substantial study sample, the adjusted 1-year risk of cancer being 1.74 to 4.72 times higher among those with vitamin

B12 levels above the upper limit of blood concentration (600 pmol/L). This increased short-term cancer risk was noted in 3.4% of people with elevated B12 levels compared to those with normal levels. After multivariable adjustments, the highest odds (4.72) were noted in those with levels above 1000 pmol/L. The conclusion is that some cancers may affect B12 metabolism (107). In another study, the use of vitamin B6 and B12 from individual supplement sources was associated with a 30% to 40% increase in lung cancer risk among males, but not females. The 10-year average supplement dose shows an almost two-fold (1.98) increase in lung cancer risk in the B12 category of > 55µg/d compared with nonusers (16). Mechanistically, vitamins B6, B9, and B12, interacting with homocysteine and methionine, participate in the so-called one-carbon metabolism pathway, an essential network of reactions of the folate and methionine cycles involved in basic cellular processes: DNA/RNA synthesis, amino acid homeostasis, redox defense, and epigenetic regulation. Disruption in this process is believed to promote carcinogenesis (3, 104).

Other studies actually report associations between lower vitamin B12 concentrations and a higher risk of certain cancers (108, 109). A study by Sun et al. found a significant non-linear inverse relationship between dietary vitamin B12 intake and colorectal cancer risk, proposing the use of vitamin B12 for cancer prevention (108). A meta-analysis of 18 randomized controlled trials showed that supplements containing B vitamins had little or no effect on cancer incidence (2). Altogether, current information underlines the need for more high-quality and dose-response research to clarify the relationship between vitamin B12 and cancer risk.

**Vitamin C (Ascorbic acid - AA)**

Humans require vitamin C from food due to the deficiency of an enzyme, l-gulono-γ-lactone oxidase, a key enzyme for ascorbic acid biosynthesis. The gene of this enzyme is non-functional due to mutations considered to be an evolutionary event against oxidative stress (110). Vitamin C is a powerful water-soluble antioxidant that regenerates other antioxidants (*e.g.,* vitamin E) and protects against lipid peroxidation, reactive nitrogen oxide, superoxide radical anion, hydroxyl radical, and singlet oxygen. Besides, it is involved in a variety of biosynthetic pathways, such as collagen synthesis, hydroxylation of dopamine to norepinephrine, histone demethylation, and many others (111-113).

Intestinal absorption of vitamin C is tightly controlled. The maximal absorption, up to 90%, is achieved with moderate intake levels of about 100 mg/day. When doses are above 1 g/day, the absorption falls

by 50%, which gives a peak plasma concentration of around 135 µmol/L. The maximal tolerated vitamin C oral dose of 3g/4h predicted peak plasma concentrations of only 220 µmol/L (112, 114).

Tissue capacity to retain and recycle vitamin C is substantial. It is estimated that the extracellular pool contains 150 mg and the intracellular pool 1.5g of vitamin C. It is eliminated through the kidneys with an average 24h urinary excretion of 20 mg vitamin C and 30 mg oxalate. Approximately 60 mg of the vitamin is non-enzymatically degraded each day to form oxalate (~ 30mg). Additionally, pathways that do not form oxalate are indicated (110). The oxidized form of vitamin C, dehydroascorbic acid (DHA), is partially and irreversibly transformed to diketogulonic acid (DKG), which is broken down to oxalate. But it is unknown how much DKA is formed and further converted to oxalate. Certainly, genetic and environmental factors influence these metabolic pathways, as well as kidney function (115).

As there is a maximum for intestinal absorption, with oral doses over 1g/day, a significant part is not absorbed, and another part is excreted unchanged in urine. Thus, in order to achieve therapeutic plasma levels, vitamin C must be administered intravenously. Such treatments are performed in cancer patients and infections, but with variable and sometimes questionable results (38, 110, 114).

An acute high-dose intake of vitamin C can cause digestive problems. This is the result of vitamin C's osmotic action, and the effect can range from mild, such as abdominal discomfort, to moderate-severe, such as nausea, diarrhea, cramps, headache, and faintness. Therefore, a tolerable upper limit of 2,000 mg/day has been established. In addition, vitamin C can promote iron absorption, impair the absorption of vitamin B12 and copper, and when applied to the skin, vitamin C preparations may cause irritation (4, 116, 117).

Increased vitamin C intake through supplements for a prolonged period is a significant risk factor for the development of kidney stones. Daily consumption of vitamin C supplements (1-10g) for extended periods increases urinary oxalate excretion. Among several factors analyzed (dietary calcium, oxalate, animal protein, vitamin C, vitamin B6, potassium, and sodium in urine), vitamin C had the greatest impact on urinary oxalate excretion (118). It is reported that a small increase in dietary vitamin C intake (~ 100 mg) may increase stone risk, while those consuming large oral doses develop oxalate nephropathy (110, 118).

However, most people do not require vitamin C supplementation. It doesn't have a prophylactic effect against cold, although it may speed up recovery (days confined to home and off work). Routine mega-dose prophylaxis is not justified for common use (119, 120). In in vitro conditions, vitamin C doses of

0,075-0,175 ng stimulated mitogen-induced blast transformation of T and B lymphocyte primary cultures (2,5 x $10^5$ cells). However, progressively higher concentrations showed an inhibitory effect on lymphocyte proliferation (121).

The vitamin C effects have been extensively studied in many cell types. It was demonstrated that when in high concentrations, it mediates toxic effects on normal and cancer stem cells. This was achieved through generating excessive ROS and hindering energetic homeostasis. Undifferentiated neural stem/progenitor cells (NSPCs) were more sensitive to vitamin C-driven DNA damage than differentiated cells. Similarly, high-dose vitamin C significantly damaged cancer stem cells compared to differentiated tumor cells. This and other studies led to recognition of vitamin C as a potential anti-tumor agent. Nevertheless, excessive vitamin C doses might interfere with the healthy antioxidant-prooxidant balance in the body (1, 122, 123). An intake exceeding 2 grams per day can create an environment that induces oxidative stress. Vitamin C can have a prooxidant effect in case of high dose (1000 mg/kg body weight) or when combined with iron or copper, thereby creating reducing cycles through the Fenton reaction. Also, when in combination with other antioxidant vitamins, it may provoke mild oxidative stress (113, 124). Nevertheless, recent research argues that even pro-oxidant actions may have beneficial effects on cellular adaptations and survival. Despite observed elevated levels of DNA damage biomarkers, such as 8-oxoG (one of the most common DNA lesions resulting from ROS and leading to mismatched pairing), it is proposed that vitamin C promotes 8-oxoG removal by upregulation of repair enzymes thanks to its pro-oxidant properties (117).

**Conclusion**

Current research shows an ample amount of new evidence about biological and pathological properties produced by excessive intake of water-soluble vitamins, which are traditionally considered to be safe. There are an increasing number of case reports, critical reviews, and meta-analyses that provide necessary information about vitamin supplementation and a widening spectrum of overdose-related signs and symptoms, as well as explanatory mechanisms. Most people do not need to supplement with over-the-counter vitamins when consuming sufficient and varied nutrition. Experts recommend restricting the use of pharmaceutical forms of vitamins without professional consultation. Research data put a highlight on a 'U-shaped' relationship between multivitamin supplementation and adverse health risks, with both low and high intake being associated with disease development. Taking the advice of

medical professionals can limit the likelihood of adverse effects from consuming vitamin supplements, including water-soluble forms.

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