Continuing Education

Supplements: Overview and Treatment Options

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Objectives:

At the completion of this activity, the participant will be able to:

- Name at least four of the most common vitamin/mineral deficiencies seen in community pharmacies.
- List at least three common vitamin/minerals that can directly affect blood formation and describe their primary involvement in these processes.
- Name two common vitamin/minerals that affect bone metabolism and bone health.
- Identify two minerals abundant in the body that have major impact involving nerve, muscle and cardiovascular functions.

Supplements: Overview and Treatment Options

Introduction

The human body requires many different vitamins, hormones and trace minerals that are crucial for both body development, function and preventing disease. Some are produced naturally while others are required from exogenous sources such as diet.[1] A nutritional deficiency occurs when the body does not absorb or obtain the dietary intake necessary for a certain nutrient. Deficiencies can lead to a variety of health problems. These can include digestion problems, skin disorders, stunted or defective bone growth, heart problems and more. The amount of each nutrient one should consume depends on his or her age. In the United States, many foods bought in the grocery store (such as cereals, bread, and milk) are fortified with nutrients that are necessary to prevent nutritional deficiency.[1,2] Sometimes one's body is unable to absorb certain nutrients, even if consuming the proper amount, thus requiring supplementation. Some of the most common deficiencies seen in community pharmacies are calcium, vitamin D, potassium, iron, vitamin B-12, folate, and magnesium.[2]

Calcium

The most abundant cation in the body is calcium accounting for 1% to 2% of adult human body weight.[3] Over 99% of total body calcium is found in teeth and bones. The remainder is present in blood, extracellular fluid, muscle, and other tissues. Calcium is important for several reasons. Calcium activates a number of enzymes and is required for acetylcholine synthesis.[3] Calcium also increases cell membrane permeability, aids in B-12 absorption, regulates muscle relaxation and contraction, and plays a role in plasma clotting factors. Extracellular calcium concentrations are maintained through a series of feedback mechanisms that involve parathyroid hormone (PTH) and the active vitamin D metabolite.[3,4] There are multiple causes for low calcium levels including inadequate dietary intake, decreased fractional calcium absorption, enhanced calcium excretion, impaired PTH production and impaired vitamin D production (refer to Table 1).[3-5]

Table 1. Causes of Calcium Deficiencies[3,4]

Hormone	Effect on Calcium	Net Effect
Parathyroid hormone (PTH)	• Promotes absorption of calcium in the intestines • Increases calcium reabsorption in the distal tubules • Stimulates the release of vitamin D	Increases calcium levels
Vitamin D	• Increases intestinal absorption of calcium • Increased calcium reabsorption in the proximal tubules • Activates osteoclasts to mobilize calcium from the bones	Increases calcium levels

Patients with hypocalcemia may be asymptomatic if the decrease in serum calcium is relatively mild; however, patients with severe hypocalcemia may present with life-threatening symptoms.[3] Moderate to severe hypocalcemia is commonly associated with paresthesia or tingling, usually of the fingers and toes.[4,5] However, severe hypocalcemia can induce seizures, bronchospasm, and prolongation of the QT interval.[4] Hypocalcemia is commonly defined as serum calcium level lower than 8.2 mg/dL (2.05 mmol/L) or an ionized calcium level lower than 4.4 mg/dL (1.1 mmol/L).[5] The primary source of calcium is in one's diet, for example milk and other dairy products, such as hard cheese, cottage cheese, or yogurt. Some cereals, green vegetables, soy products, and fruit juices are also fortified with calcium. Nevertheless, if dietary intake cannot be increased to achieve adequate levels of calcium, supplements can be used.

There are multiple forms of calcium supplements (calcium carbonate, calcium gluconate, calcium citrate, and calcium lactate), the most common oral supplements are calcium carbonate and calcium citrate.[5,6] Calcium carbonate is more commonly available and is both inexpensive and convenient. Calcium carbonate is absorbed best when taken with food, due to its dependence on stomach acid for absorption. There are many natural calcium carbonate forms such as oyster shells and coral, but these products should not be recommended because of concerns for high concentrations of lead and other heavy metals. The primary issue with calcium carbonate is the poor absorption predominantly with elderly patients. Calcium citrate does not depend on acid; therefore, does not need to be administered with meals. Calcium citrate is the preferred formulation in elderly patients due to better absorption when compared to calcium carbonate. The dose of the calcium supplement should be based on age, refer to Table 2.[7] For example, post-menopausal women require 1,200 mg of calcium daily while adult men only require 1,000 mg. Furthermore, calcium products come in alternative dosage forms (eg, chews, dissolvable tablet, and liquid), which can be beneficial for select patients.

Table 2. Recommended and Upper Limits of Calcium[7]

Age	Recommended Dietary Allowance (mg/day)	Upper Level Intake (mg/day)
9-18	1,300	3,000
19-70	1,000 (for males); 1,200 (for post-menopausal women)	2,500
>70		2,000

Calcium's most common adverse reaction, constipation, can first be treated with increased water intake, dietary fiber, and exercise. If constipation persist, smaller and more frequent administration or decreasing the total daily dose can be attempted to relieve the constipation.[7] Calcium carbonate can create gas and cause stomach upset, which might resolve with calcium citrate, a product with fewer GI side effects.[4,5] The increased risk for kidney stones is controversial, clinical trials have shown no effect up to a 17% increase in kidney stones.[8-10] Increased fluid intake and decreased salt intake can decrease the risk of developing kidney stones. Calcium supplements can interact with absorption of some drugs including iron, tetracyclines, fluoroquinolones, bisphosphonates, and thyroid supplements.[5]

Patients with acute symptomatic hypocalcemia (calcium level lower than 7.0 mg/dL, ionized calcium level lower than 0.8 mmol/L) should be treated promptly with intravenous (IV) calcium.[3-4,7] Calcium gluconate is preferred over calcium chloride because it causes less tissue necrosis if extravasation occurs. Serum calcium concentration should be monitored weekly at first and then at three month intervals after calcium concentrations have stabilized. The serum calcium level should be targeted to about 8.0 mg/dL. Calcium alone does not prevent fractures, but when combined with vitamin D, it decreases fractures by 11% to

15%, vertebral fractures by 16%, and hip fractures by up to 30%.[6,8-9]

Vitamin D

Vitamin D, which has properties of both a vitamin and a hormone, is necessary for the proper formation of bones and for mineral homeostasis.[11-13] Some factors that can increase the risk for vitamin D deficiency are obesity, heredity disorders of vitamin D metabolism, chronic renal failure, inadequate sunlight exposure, dark skin pigmentation, and dietary habits like following a vegan diet.[11] Vitamin D's main function is in the regulation of calcium absorption and homeostasis.[11-12] Although vitamin D is commonly known to help with bone and mineral metabolism, it also been found to be beneficial for health in general. Without sufficient vitamin D, bones can become thin and brittle. A level above 10 ng/mL is necessary for preventing rickets or osteomalacia. However, prospective trial data indicate that a higher level, such as 20–30 ng/mL, is required to optimize intestinal calcium absorption, maintenance of bone mass, reduce falls and fractures, and prevent a wide variety of diseases including diabetes mellitus, hyperparathyroidism, autoimmune diseases, and cancer.[11-12] An expert panel for the Institute of Medicine (IOM) has recently recommended that a level of 20 ng/mL (50 nM) was sufficient, although up to 50 ng/mL (125 nM) was considered safe.[13] Table 3 provides information on health status in relation to vitamin D levels.[14]

Table 3: Vitamin D [25(OH)D] Concentrations and Health Status[14]

nmol/L	ng/mL	Health Status
<30	<12	Associated with vitamin D deficiency, leading to rickets in infants and children and osteomalacia in adults
30 to <50	12 to <20	Generally considered inadequate for bone and overall health in healthy individuals
≥ 50	≥ 20	Generally considered adequate for bone and overall health in healthy individuals
> 125	> 50	Emerging evidence links potential adverse effects to such high levels, particularly >150 nmol/L (>60 ng/mL)

*1 nmol/L = 0.4 ng/mL

The signs and symptoms of vitamin D deficiency include abnormal calcium levels, muscle weakness, increase number of falls, and an increase in cardiovascular risk.[12] For individuals between the ages of 1 and 70 years, 400-800 international units (IU) daily vitamin D is thought to be sufficient to meet recommended dietary allowances, while up to 4000 IU daily is considered safe. These recommendations are based primarily on data from randomized placebo-controlled clinical trials (RCT) that evaluated falls and fractures.[12-13] There are many types of vitamin D preparations available for the treatment of vitamin D deficiency or insufficiency. The two commonly available forms of vitamin D supplements are ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3).[13,15-16] Vitamin D3 is the most popular option when possible, rather than vitamin D2, because vitamin D3 is the active form of vitamin D and also raises vitamin D levels more effectively.[15-16] For patients with vitamin D levels <10 ng/mL (25 nmol/L), treatment usually includes 50,000 IU vitamin D2 or D3 by mouth once or more per week for six to eight weeks, and then 800 to 1000 IU of vitamin D3 daily thereafter.[13,15-16] For patients with levels of 10 to 20 ng/mL (25 to 50 nmol/L), treatment usually includes 800 to 1000 IU of vitamin D3 by mouth daily. Once a normal level is achieved, continued therapy with 800 IU of vitamin D per day is usually recommended.[15] Furthermore, with levels of 20 to 30 ng/mL (50 to 75 nmol/L) treatment with 600 to 800 IU of

vitamin D3 by mouth daily may be sufficient to maintain levels in the target range. Side effects of vitamin D are uncommon unless levels becomes very elevated. If levels do become greater than 100 ng/mL or 250 mmol/L, complications such as hypercalcemia or kidney stones can develop.[17-18] A blood test is recommended to monitor blood levels of vitamin D three months after beginning treatment. The dose of vitamin D may need to be adjusted based on these results and subsequent blood levels of vitamin D every three to six months should be obtained to assure that normal levels result from the adjusted dose. [16]

Potassium

Potassium is the most abundant intracellular ion in the body.[19] The total body stores roughly 3,000-4,000 mEq of potassium. About 2% of that is pumped out by the sodium-potassium-adenosine triphosphatase (Na+-K-ATPase) to the extracellular compartment, which should be 3.5 to 5 mEq/L.[19] An average of 90% of the daily intake of potassium is excreted by the kidneys, thus playing a crucial role in the regulation of serum potassium. Dietary intake, renal excretion, acid-base balance, aldosterone, and insulin all play a crucial role in the amount of potassium in the body at any given time. Changes in the exchange or distribution of intra- or extracellular levels of this ion can lead to hypokalemia or hyperkalemia.[19-21] Table 4 provides the potassium serum levels that correlate with the severity of hypo- or hyperkalemia.

Table 4. Severity of Hypokalemia and Hyperkalemia [21]

Severity	Hypokalemia	Hyperkalemia
Mild	3-3.5 mEq/L	5.5-6 mEq/L
Moderate	2.5-3 mEq/L	6.1-6.9 mEq/L
Severe	<2.5 mEq/L	>7 mEq/L

Hypokalemia describes a serum potassium level less than 3.5 mEq/L. Hypokalemia occurs in about 20% of hospitalized patients and is associated with a 10-fold increase in hospital mortality.[19] Low potassium levels have been shown to change cardiac rhythm (ventricular and atrial arrhythmias), blood pressure, and cardiovascular mortality depending on the severity of hypokalemia. Hypokalemia can be caused by a multitude of conditions including decreased dietary intake, excessive potassium loss from digestive tract (diarrhea, vomiting), chronic kidney disease, magnesium deficiency, and certain medications (eg, diuretics, beta agonist, laxatives and insulin).[21-22]

Goals of treatment are to correct the low potassium levels and/or treat the underlying cause.[21] Whenever possible, potassium supplementation should be administered by the oral route. Three salts are available for oral potassium supplementation: chloride, phosphate, and bicarbonate. Potassium phosphate is generally reserved for patients who are experiencing both low potassium and phosphorous levels. [22] Potassium bicarbonate is most commonly used when potassium reduction occurs in the setting of metabolic acidosis. Potassium chloride, however, is the most common and effective salt form used for the most common causes of potassium depletion.[21-22] The general rule for supplementing potassium is for every 10 mEq given, an increase of 0.1 mEq/L is seen. Patient's dosing will depend on the severity of the hypokalemia. Patients with mild-moderate hypokalemia should receive 40-100 mEq of potassium once daily in divided doses. Nevertheless, patients with severe hypokalemia (<2.5 mEq/L) should receive 40 mEq of potassium three to four times a day.[20]

Patients should be counseled to take potassium supplements with meals to avoid the gastrointestinal irritation, such as upset stomach, indigestion, nausea, vomiting and gas, that is associated with these supplements.[17] Potassium levels, as well as, renal function should be monitored every 1 to 2 months in stable patients. Close monitoring of potassium levels are required, due to the severity of hypo- and hyperkalemia.[17]

Hyperkalemia is defined as a serum potassium level greater than 5.5 mEq/L and occurs in 10% of hospitalized patients.[19] Most cases of hyperkalemia is due to the overcorrection of hypokalemia with IV potassium supplements. Other causes include a decrease in renal excretion, increased dietary intake, intra-to extracellular shift, and certain medications (angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blockers (ARBs), direct renin inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), potassium-sparing diuretics, and aldosterone antagonists).[23] Hyperkalemia is a medical emergency due to the effects it can have on the heart such as sinus bradycardia, sinus arrest, ventricular tachycardia, and ventricular fibrillation.[19] The treatment for this disorder is potassium restriction or pharmacotherapy. Refer to Table 5 for information on the potential pharmacological treatments of hyperkalemia.[22] Monitoring is weekly if outpatient and daily if inpatient.

Table 5: Treatment for Hyperkalemia[22]

Medication	Dose	Route
Calcium	1 g	IV over 5-10 min
Furosemide	20-40 mg	IV
Dextrose	10%: 1,000mL (100g) 50%: 50 mL (25g)	10%: IV over 1-2 hours 50%: IV over 5 minutes
Regular Insulin	5-10 units	IV or SQ
Sodium bicarbonate	50-100 mEq	IV over 2-5 minutes
Albuterol	10-20 mg	Nebulized over 10 minutes

Iron

More than a quarter of the world's population is anemic, with about one-half of the burden from iron deficiency.[24] Iron is a mineral that is found in many foods and supplements.[25] Iron is an essential component of hemoglobin, an erythrocyte protein that transports oxygen. Dietary iron comes in two forms: heme and non-heme. Heme iron has a higher bioavailability than non-heme iron.[25] Ascorbic acid helps the absorption of non-heme iron and can be found in certain supplements, as well as, diet. Meats, seafood, and poultry have both forms, whereas, plants and other foods such as nuts, beans, and vegetables contain non-heme only. Iron's bioavailability is about 14-18% from diet alone.

Iron deficiency occurs in over one-third of the world's population and is the most common form of malnutrition.[24-26] Certain persons who are at an increased risk for iron deficiency are children 0-5 years of age, women in childbearing age, and pregnant women.[26] Certain conditions can also increase a person's risk of developing iron deficiency such as chronic kidney disease, irritable bowel syndrome, heart failure, and cancer (see Table 6).[27]

Causes of Iron Deficiency	Conditions that Cause Deficiency
Increased demand for iron	• Rapid growth during adolescence • Pregnancy • Erythropoietin therapy
Increased iron loss	• Chronic blood loss • Acute blood loss • Menses • Blood donation • Phlebotomy as treatment for polycythemia vera
Decreased iron absorption	• Inadequate diet • Malabsorption from disease (sprue, Crohn's disease) • Malabsorption from surgery (gastrectomy and some forms of bariatric surgery) • Acute or chronic inflammation

Iron deficiency progression can be divided into 3 stages: negative ion balance, iron-deficient erythropoiesis, and iron-deficient anemia.[28] When looking at labs for a patient, the total iron binding capacity (TIBC), serum iron, and transferrin saturation (t-sat) are the most pertinent lab values.[29] One can calculate the t-sat from the TIBC and serum iron (serum iron/TIBC).[29] Refer to Table 7 to correlate the progression of each stage of iron deficiency to the laboratory values being monitored for iron.[28]

Table 7. Iron Lab Values with Iron Deficiency Stage Progression[28]

Parameter	Normal	Negative Ion Balance	Iron-Deficient Erythropoiesis	Iron-Deficiency Anemia
Serum ferritin	50-200	<20	<15	<15
Total iron binding capacity (TIBC)	300-360	>360	>380	>400
Serum iron	50-150	Normal	<50	<30
Transferrin saturation	30-50	Normal	<20	<20
RBC protoporphyrin	30-50	Normal	>50	>50
Soluble transferring receptor	4-9	>9	>9	>9
RBC morphology	Normal	Normal	Normal	Microcytic Hypochromic

A number of patients with iron deficiency anemia will remain asymptomatic while others will have symptoms including weakness, paleness, headache, decreased exercise tolerance, fatigue, irritability, and depression.[25] More severe symptoms of iron deficiency include neurodevelopmental delay (especially in children), pica, pagophagia (ice craving), alopecia, restless legs syndrome, cardiac murmur, tachycardia, and atrophic glossitis.[25] Treatment of iron deficiency and iron deficiency anemia involves more than merely replacing iron. In all patients, the cause of iron deficiency must be identified and addressed. The choice between oral and intravenous iron depends on a number of factors including the severity of the anemia, costs and availability of different iron replacement products. Most patients are treated with oral iron because it is generally effective, readily available, inexpensive, and safe.[26-27]

Multiple variations of iron are on the market, ranging from simple iron salts (ferrous and ferric) to complex compounds designed as a sustained release product to help with intolerable side effects.[12,17-18,27] Between ferrous and ferric salts, ferrous has a higher solubility; therefore, ferrous salts are more available than ferric formulations.[26] Iron products should be taken on an empty stomach to increase absorption.[26] Table 8 provides information on the most commonly used oral iron supplements.[24]

Table 8. Oral Iron Supplements[24]

Formulation	Brand Name Examples	Characteristics	Elemental Iron
Ferrous fumarate	Ferro-Sequels	• Similar to ferrous sulfate • 324 or 325 mg tablet	106 mg/ tablet
Ferrous gluconate	Fergon	• Similar to ferrous sulfate • 240 mg tablet • 324 mg tablet • 325 mg tablet	27 mg, 38 mg, and 39 mg/ tablet (respectively)

Formulation	Brand Name Examples	• Characteristics	Elemental Iron
Ferrous sulfate	Feosol, FeroSul	• Gold standard for supplementation, proven effective, extensive history of use • Enteric coated • Available in delayed release and enteric coated • 325 mg tablet • 195 mg tablet • 220 mg/5 mL oral elixir • 75 mg/mL oral solution	65 mg/tablet, 39 mg/tablet, 44 mg/ 5 mL, 15 mg/ 1 mL (respectively)
Polysaccharide Iron	NovaFerrum, Niferex	• Similar to ferrous sulfate • 150 mg tablet • 50 mg tablet	150 mg/tablet and 50 mg/tablet (respectively
Ferric Citrate	Iron Citrate	• Most commonly used ferric salt • Less bioavailable than ferrous salts • 210 mg tablets	38 mg/tablet

The dose of oral iron depends on patient age, severity of iron deficiency, and side effects.[12,25,28] The recommended daily dose for the treatment of iron deficiency in most adults is 150 to 200 mg of elemental iron daily.[26] The most common side effects are abdominal pain, nausea, and constipation, but small doses of iron or choosing a sustained release formation may improve these symptoms.[25,29] Older individuals may have a higher chance of side effects from oral iron and may be treated with a lower dose. In a randomized study including 90 hospitalized patients greater than 80 years of age who had iron deficiency, daily doses of 15, 50, or 150 mg of elemental iron for two months were shown equally effective in raising hemoglobin and ferritin concentrations, while adverse side effects were significantly less common at the lower iron doses.[30] To reduce the prevalence of side effects one can reduce the dose, increase the dose interval time, or take the supplement with food. It is also important to note that iron has many drug interactions. Iron should be taken two hours after or six hours before antacids, fluoroquinolones, tetracyclines, and thyroid products to avoid decreasing these medications' efficacy.[17-18,25]

Regardless of the presence of symptoms, all patients with iron deficiency anemia and most patients with iron deficiency without anemia should be treated. Monitoring of patients receiving iron replacement depends on the severity of anemia. Patients receiving oral iron should be re-evaluated two weeks after starting therapy.[17]

Vitamin B-12

Vitamin B-12 (cobalamin) is a water-soluble vitamin that is vital to normal neurologic function, red blood cell production, and DNA synthesis.[31] Vitamin B-12 contains the mineral cobalt that is present in several forms that are active in human metabolism. It is synthesized by microorganisms and found in the liver. It is hydrolyzed by the gastric cells in the stomach, binds to an intrinsic factor so it can be absorbed by the intestines. If a person is taking a supplement, the vitamin B-12 is "free" and therefore, does not go through hydroxylation. It goes directly into the stomach, binds the intrinsic factor, and immediately into intestines for absorption.[32] This vitamin is mostly found in animal products such as fish, meat, eggs, and milk. Vitamin B-12 deficiency is a common cause of megaloblastic anemia, a variety of neuropsychiatric symptoms, and elevated serum homocysteine levels, especially in elderly patients.[33] There are a number of risk factors for vitamin B-12 deficiency including age (older

adults), pernicious anemia, gastrointestinal disorders, surgery, vegetarians, and pregnant and lactating women.[33] Prolonged use of metformin, proton pump inhibitors, and histamine blockers can also lead to vitamin B-12 deficiency (see Table 9).[34]

Table 9. Risk Factors for Vitamin B-12 Deficiency[34]	
Decreased intake	Alcoholics Elderly Vegetarians
Medications	Histamine H2 blockers Proton pump inhibitors Metformin
Decreased intrinsic factor	Atrophic gastritis Pernicious anemia
Conditions	Crohn's disease Ileal resection Tapeworm infestation Post GI surgery

Normal B-12 serum levels range from 200-900 pg/mL.[32] B-12 deficiency is defined as a measurement below 200 pg/mL. Measurements of serum vitamin B-12 may not reliably detect deficiency, and measurement of serum homocysteine and/or methylmalonic acid should be used to confirm deficiency in asymptomatic high-risk patients with low normal levels of vitamin B-12.[32] Symptoms include fatigue, weakness, constipation, loss of appetite, weight loss, numbness in the hands, and even neurological changes (see Table 10 for a comprehensive list).[34]

Table 10. Clinical Manifestations of Vitamin B-12 Deficiency[34]
Hyperpigmentation
Glossitis
Jaundice
Anemia (macrocytic, megaloblastic)
Thrombocytopenia
Cognitive impairment
Gait abnormalities
Irritability
Peripheral neuropathy
Weakness

Typically, the deficiency is treated with B-12 injections to bypass anything that may decrease the GI absorption; however, high doses of oral therapy is also effective.[33] Oral administration of high-dose vitamin B-12 (1 to 2 mg daily) is as effective as intramuscular administration in correcting the deficiency, regardless of etiology; however, oral absorption depends on sufficient intrinsic factor being present.[33] Because crystalline formulations are better absorbed than naturally occurring vitamin B-12, patients older than 50 years and strict vegetarians should consume foods fortified with vitamin B-12 and vitamin B-12 supplements, rather than attempting to get vitamin B-12 strictly from dietary sources.[35] Vitamin B-12 formulations include tablets, lozenges, sublingual tablets and drops all available over-the-counter.[33] The intramuscular injection requires a prescription. Adverse effects of B-12 supplementation are arthralgia, dizziness, headache, and nasopharyngitis.[36] Monitor levels one month after treatment and then 3-6 months thereafter.[17]

Folate

Folic acid deficiency is one of the most common vitamin deficiencies occurring in the United States, largely because of its association with excessive alcohol intake and pregnancy.[31,37] Folate is a B-9 vitamin naturally present in many foods that plays a crucial role in the body.[31] Folate is known synthetically as folic acid, which is used to supplement many dietary compounds and foods.[37] The form of folate that can enter the main folate metabolic cycle is tetrahydrofolate (THF). Unlike natural folates, which are metabolized to THF, folic acid undergoes initial reduction and methylation in the liver, where conversion to the THF form requires di-hydrofolate reductase.[37-38] Folate is essential in our body's ability to make DNA and other genetic material. Folate also has an important role in cell division, which makes it especially important in infancy and pregnancy that the recommended daily dose is consumed,

which is different depending on a person's age.[31]

Folate is necessary for the production of DNA and RNA.[37] The most common laboratory-identified feature of folic acid deficiency is megaloblastic anemia.[37-39] Megaloblastic anemia specifically is a disorder where red blood cells are larger than normal and not fully developed.[31] It causes weakness, fatigue, trouble concentrating, irritability, headache, heart palpitations, and shortness of breath. Folate deficiency can also cause open sores on the tongue and inside the mouth as well as changes in the color of the skin, hair, and fingernails.[31] In addition, pregnant women who do not get enough folate are at risk of having babies with neural tube defects, such as spina bifida. Folate deficiency can also increase the likelihood of having a premature or low-birth-weight baby.[37]

Folate deficiency can occur for multiple reasons, one of which is not enough folate in your diet. Folic acid is a water-soluble vitamin; thus, not stored in the fat tissues of the body. Excess amounts of the vitamin leave the body through the urine. Because folate is not stored in the body in large amounts, blood levels will become low after only a few weeks of eating a diet low in folate.[40-41] A folate deficiency may also occur if you have a disease or genetic mutation that prevents absorbing or converting folate to its usable form. Certain groups of people are more susceptible to acquiring a folate deficiency. These groups include teen girls ages 14-30, especially before and during pregnancy, non-Hispanic black women, people with alcoholism, and people who may have difficulty in regards to nutrient absorption, such as those with celiac disease and inflammatory bowel disease. Medications can also cause folate deficiency including phenytoin (Dilantin), trimethoprim-sulfamethoxazole, methotrexate, and sulfasalazine.[31,37] The results of folic acid measurements vary depending on the assay method used. Decreased serum folic acid levels (less than 4 ng/mL [less than 9 nmol/L]) indicate a folate deficiency megaloblastic anemia that may coexist with a vitamin B-12 deficiency anemia.[37,40]

Once diagnosed with a folate deficiency, patients should attempt to add through dietary means, however if this is not effective, supplements should be utilized. Most people in the United States get the recommended 400 mcg of folate in their diet through foods, conversely this number is lower for pediatric patients.[37,40-42] Folate is naturally present in foods such as certain vegetables, fruits and fruit juices (oranges and orange juice), nuts, beans, and peas (such as peanuts, black-eyed peas, and kidney beans), and grains (whole grains, fortified cold cereals, enriched flour products such as bread/pasta/rice). A small amount of folate is available in certain animal foods such as poultry, seafood, eggs, and dairy. In most cases, 1 mg daily is sufficient to replace folate loss, except in cases of deficiency due to malabsorption, in which case doses of 1 to 5 mg daily may be necessary.[37] Another case where a higher amount of folic acid is required is if a woman previously gave birth to a child with neural tube defects or has a family history of neural tube defects. Women meeting the previous criteria should consume 4 mg of folic acid daily.[37,45-47]

Table 11. Daily Recommended Amount of Folate[42]

Life Stage	Recommended Amount*
Birth to 6 months	65 mcg DFE
7–12 months	80 mcg DFE
1–3 years	150 mcg DFE
4–8 years	200 mcg DFE
9–13 years	300 mcg DFE
> 14 years	400 mcg DFE
Pregnant teens & women	600 mcg DFE
Breastfeeding teens & women	500 mcg DFE

*The amount of folate a person needs depends on their age, and is measured in micrograms (mcg) of dietary folate equivalents (DFEs).

1 mcg DFE = 1 mcg food folate
1 mcg DFE = 0.6 mcg folic acid from fortified foods or dietary supplements consumed with foods
1 mcg DFE = 0.5 mcg folic acid from dietary supplements taken on an empty stomach

Folate may cause bitter taste, bloating, changes in urine color, confusion, cramps, diarrhea, dizziness, fatigue, gas, increased cancer risk, increased seizure frequency, inflammation (such as in the mouth), lung muscle spasms, mood swings (excitability or irritability), vivid dreaming, and weight changes.[17-18,37] The upper limits for folic acid are listed below in Table 12.[42] Nevertheless, folic acid toxicity is rare due to folate being water soluble and having rapid excretion.[37,43-44]

Table 12. Upper Limits per Day of Folate[42]

Ages	Upper Limit
Birth to 6 months	Not established
Infants 7–12 months	Not established
Children 1–3 years	300 mcg
Children 4–8 years	400 mcg
Children 9–13 years	600 mcg
Teens 14–18 years	800 mcg
Adults	1,000 mcg

Maintenance therapy can typically be stopped after 1-4 months if the patient has at least one fresh fruit or vegetable daily. For patients with chronic malabsorption diseases, folic acid supplementation may be needed lifelong.[42]

Magnesium

Magnesium is the fourth most abundant essential mineral in the body.[48] Magnesium is distributed approximately one half in the bone, one half in the muscle and other soft tissues, and less than 1% is in the blood. Magnesium is a cofactor in more than 300 enzyme systems that regulate a variety of biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation.[49-50] Magnesium is required for energy production, oxidative phosphorylation, and glycolysis. It contributes to the structural development of bone and is required for the synthesis of DNA and RNA. Magnesium also plays a role in the active transport of calcium and potassium ions, which has a vital role in nerve impulse conduction, muscle contraction, and normal heart rhythm.[49-50] Conditions that may increase the risk of magnesium deficiency include: poorly-controlled diabetes mellitus, chronic malabsorption problems such as Crohn's disease, medication use (diuretics, antibiotics), chronic alcoholism, and older age due to decreased absorption of magnesium and increased renal exertion.[50-51]

Early signs of magnesium deficiency include loss of appetite, nausea, vomiting, fatigue, and weakness.[51-52] As magnesium deficiency worsens, numbness, tingling, muscle contractions and cramps, seizures, personality changes, abnormal heart rhythms, and coronary spasms can occur.[49,51] Severe magnesium deficiency can result in hypocalcemia or hypokalemia because the mineral homeostasis is disrupted.[52] A deficiency in magnesium can lead to inflammation which is associated with multiple major health conditions such as heart disease, diabetes, and certain cancers. There are many challenges in diagnosing magnesium deficiency due to its distribution in the body. Magnesium is an intracellular cation and its blood concentrations may not accurately reflect magnesium status.[49,51] Hypomagnesemia is defined as having magnesium levels that are less than 1.8 mg/dL.[49,52] Symptoms of magnesium deficiency do not usually manifest until magnesium levels have dropped to less than 1.2 mg/dL. Magnesium homeostasis is largely controlled by the kidney, which typically excretes about 120 mg magnesium into the urine each day.[53] Urinary excretion is reduced when magnesium status is low. Once low magnesium is confirmed it is important to begin treatment immediately. Low magnesium levels can ultimately cause low calcium levels, increasing the patient's risk to have negative effects accompanying the deficiencies.

There are several options to treat low magnesium. The first option is increase magnesium intake through the diet. Green leafy vegetables, such as spinach, legumes, nuts, seeds, and whole grains, are good sources for

magnesium.[52] However, for those not able to reach normal magnesium levels, supplements are available in a variety of forms, including magnesium oxide, aspartate, sulfate, citrate, and chloride.[54-57] Magnesium has been used for numerous conditions such as preeclampsia, arrhythmias, asthma, headache, dyspepsia, and constipation.[52] Small studies have found that magnesium in the aspartate, citrate, lactate, and chloride forms is absorbed more completely and is more bioavailable than magnesium oxide and magnesium sulfate.[54-57] One study found that very high doses of zinc from supplements (142 mg/day) can interfere with magnesium absorption and disrupt the magnesium balance in the body.[56] In Table 13 one can find the recommended dietary and supplemental amount of magnesium that should be taken daily for magnesium deficiency.[49,51-52]

Table 13. Recommended Dietary and Supplemental Amounts of Magnesium[49,51-52]

Recommended Dietary Allowances			Tolerable Upper Intake Limits for Supplements	
Age	Male	Female	Male	Female
9-13	240 mg	240 mg	350 mg	350 mg
14-18	410 mg	360 mg		
19-30	400 mg	310 mg		
> 30	420 mg	320 mg		

Several preparations are available for supplementation. Some of the more commonly used supplements include Mag-Ox 400 (magnesium oxide), Slow-Mag (magnesium chloride), and Mag-Tab (magnesium lactate).[17-18,52] These preparations provide 60-84 mg of magnesium per tablet. The amount of tablets needed depends on the severity of the deficiency, for example patients with severe hypomagnesemia will need closer to the upper limits than one with moderate hypomagnesemia.[49,51-52] Too much magnesium from food does not pose a health risk in healthy individuals because the kidneys eliminate excess amounts in the urine.[2] However, high doses of magnesium from dietary supplements or medications often result in diarrhea, nausea and abdominal cramping.[17-18,52] Symptoms of magnesium toxicity, usually develop after serum concentrations exceed 1.74–2.61 mmol/L, can include hypotension, nausea, vomiting, facial flushing, retention of urine, and lethargy before progressing to muscle weakness, difficulty breathing, extreme hypotension, irregular heartbeat, and cardiac arrest.[49,51-52] The risk of magnesium toxicity increases with impaired renal function or kidney failure because the ability to remove excess magnesium is reduced or lost.[49]

In summary, the majority of patients with vitamin deficiencies can be treated with eating a balanced diet, foods fortified with minerals and nutrients and/or taking supplements. Each one of the vitamins, hormones and trace minerals included here are crucial for both body development and preventing disease. Whenever checking serum levels of these vitamins, hormones and trace minerals it is important to also check for underlying diseases or medications that can be causing the deficiency.

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