

Common Nutrient Depletions Caused by Pharmaceuticals

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Pharmaceutical and nutrient interactions have been moderately studied yet often ignored by health care professionals. Many extensively prescribed drugs can lead to decreased absorption or increased excretion of many necessary vitamins, minerals, and amino acids. These drugs may also alter biochemical pathways necessary for proper utilization of nutrients.

According to the Centers for Disease Control and Prevention (CDC), the number of adults ages 55–64 taking at least one pharmaceutical in the previous month rose from 62 percent in 1988–1994 to 73 percent in 1999–2002.¹ The large number of individuals taking pharmaceuticals suggests that the potential for drug–nutrient interactions is substantial and growing. Owing to the vast number of pharmaceuticals on the market, this article is limited to a select group of commonly prescribed medications.

Common Pharmaceuticals That Deplete Nutrients

Estrogen and Progestins

Hormone replacement therapy (HRT) is a common prescription for menopausal women. These estrogen/progestin combinations are used to decrease symptoms associated with menopause, such as hot flashes, vaginal dryness, sleep disturbances, and fatigue. In the United States, from 1999 to 2002, approximately 15 million women were on HRT, annually accounting for 90 million prescriptions per year.²

The Women's Health Initiative study was widely publicized in 2002; this study demonstrated that HRT increases the risk of coronary heart disease, breast cancer, and strokes.³ Following the publication of the study, HRT prescriptions decreased by approximately 32 percent in 2003.⁴

Oral contraceptive pills (OCPs) also contain estrogen/progestin combinations. OCPs have been shown to increase the risk of cardiovascular events as well as breast, cervical, and liver cancer.^{5,6}

Estrogen/progestin hormones have been shown to deplete many nutrients. Research suggests that estrogens deplete several B vitamins significantly. Oral estradiol decreases pyridoxine

(vitamin B₆) and albumin in postmenopausal women.⁷ This vitamin B₆ deficiency is believed to be associated with a disruption in tryptophan metabolism.⁸

Other research indicates that oral contraceptives deplete riboflavin (vitamin B₂), folic acid, cobalamin (vitamin B₁₂), ascorbic acid (vitamin C), and zinc.⁹ Other research indicates a decrease by 40 percent of both folic-acid and serum B₁₂ levels with oral contraceptive use.¹⁰ Clinically, lower folic-acid levels appear to correlate with increased prevalence of abnormal Papanicolaou (Pap) smear results.

In addition, studies have shown that estrogen supplementation increases magnesium uptake into bone and soft tissue, causing lowered blood magnesium levels. With low magnesium intake, this alters the calcium-to-magnesium ratio. This change in ratio can cause an increase in coagulation, which may lead to an increased risk of thrombosis that occurs with estrogen supplementation.¹¹

Acid Blockers

Proton-pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2 blockers) are commonly prescribed for treating ulcers and gastroesophageal reflux disease (GERD). Lansoprazole, or Prevacid, is a PPI that ranked third in top pharmaceutical sales in the United States in 2004.¹² Many studies indicate that these classes of drugs cause several nutrient deficiencies. Research indicates that treatment with both PPI and H2 blockers increases the risk of vitamin B₁₂ deficiency significantly in elderly patients.¹³ Studies have shown that H2 blockers decrease protein-bound (as opposed to unbound) vitamin B₁₂ absorption, owing to decreasing gastric acid and pepsin secretion and a resultant inability to cleave cobalamin.

One small study showed a 53 percent decrease in protein-bound B₁₂ absorption in individuals taking an H2 blocker.¹⁴ In addition, decreased protein-bound B₁₂ absorption would not be detected on the standard Schilling test, as it measures unbound cobalamin only.¹⁵

Research also indicates that folic-acid absorption is decreased with supplementation of H2 blockers and other antacids.¹⁶ Studies have linked H2 blockers, which decrease gastric acid secretion, with decreased absorption of iron and zinc.^{17,18} One study showed a direct correlation between

increasing dosage of cimetidine, an H₂ blocker, and decreasing dietary non-heme iron absorption ranging from 28 to 65 percent.¹⁹

Animal studies have demonstrated that cimetidine significantly decreases intestinal calcium transport.²⁰ Cimetidine also alters vitamin D metabolism by altering the enzyme vitamin D 25-hydroxylase activity.²¹ A small study performed with the PPI omeprazole demonstrated that serum levels of beta-carotene were decreased with increased gastric pH.²² These findings raise the question of the long-term potential consequence for increased risk of osteoporosis, other vitamin D-linked disease states such as various cancers and multiple sclerosis, and altered RNA and DNA production as a consequence of lowered B₁₂ and folate.

Corticosteroids

Corticosteroids are often prescribed to produce anti-inflammatory and immunosuppressant activity. Prednisone and hydrocortisone are glucocorticoids frequently prescribed to help mitigate symptoms associated with various medical conditions, including autoimmune diseases and inflammatory processes.

This class of drugs affects the absorption and excretion of several nutrients. Corticosteroid treatment has been associated with increased loss of bone-mineral density. Studies show that these drugs decrease calcium absorption and increase calcium excretion.²³

In addition, a study with individuals with chronic airway obstruction showed that long-term oral steroid therapy is associated with decreased serum magnesium levels.²⁴ Steroid medication has also been associated with hypokalemia in both animal and human studies.²⁵ Research also indicates that prednisone increases urinary excretion of potassium.²⁶ Studies with individuals with rheumatoid arthritis (RA) show that serum levels of zinc and copper are also decreased with corticosteroid treatment, and urinary excretion of zinc and copper is elevated.²⁷

Additional studies on patients with RA who received corticosteroid therapy also demonstrated a decrease in plasma selenium levels.²⁸ Although the evidence appears to be incomplete or conflicting, some studies suggest that vitamin C and vitamin levels D may be affected by corticosteroid therapy.^{29,30}

Aspirin

Aspirin is used to produce antipyretic, analgesic, and anti-inflammatory activity. Recent promotion of aspirin (e.g., Bayer Aspirin) as a prophylactic treatment to decrease platelet aggregation to prevent transient ischemic attacks, strokes, and thromboembolisms has increased the use of this over-the-counter medication.³¹

Treatment with aspirin, or acetyl salicylic acid, affects several nutrients. Many studies have shown that aspirin therapy decreases vitamin C absorption.³² Some studies also indicate that increasing aspirin dosage directly correlates to increasing ascorbic acid excretion in the urine.³³ Research also suggests that aspirin therapy causes an increase in gastric blood loss leading to a decrease in total body iron.³⁴ Evidence also shows that aspirin significantly decreases both total and bound serum folate, and increases folic-acid excretion slightly.³⁵

Antidiabetes Drugs

According to the American Diabetes Association 2005 statistics, approximately 7 percent of the U.S. population has diabetes. The organization estimates that 57 percent of adults who have diabetes take oral medication only and an additional 12 percent take insulin plus oral medication to manage the condition.³⁶

Biguanides and sulfonylureas are oral medications used to treat diabetes and affect select nutrient levels adversely. Metformin, a frequently prescribed biguanide, has been shown to deplete vitamin B₁₂ and folic acid. Studies indicate that long-term metformin therapy decreases serum vitamin B₁₂ levels significantly.

Additional studies suggest that short-term treatment with metformin increases homocysteine levels, and that B vitamins (e.g., folic acid) can moderate this response.³⁷ More specifically, serum folic-acid levels have been shown to decrease 7 percent, and vitamin B₁₂ levels decrease by 14 percent, with metformin therapy in individuals who have type 2 diabetes.³⁸ Although limited, some research also suggests that treatment with sulfonylureas increases the risk of coenzyme Q10 (CoQ10) deficiency.³⁹

Statins

Statin drugs are widely used to decrease elevated cholesterol levels and prevent atherosclerosis and coronary artery disease. The statin drug Lipitor is one of the top selling pharmaceuticals worldwide and brought in an estimated 12.2 billion dollars in sales to Pfizer in 2005.⁴⁰

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMGCoA reductase), which decreases cholesterol synthesis by inhibiting the conversion of acetyl CoA to mevalonate. Mevalonate is also necessary for the production of ubiquinone, or CoQ10. Numerous studies have demonstrated that statin drug therapy significantly decreases plasma levels of CoQ10.⁴¹ CoQ10 is necessary for mitochondrial energy production, and CoQ10 has potent antioxidant activity.⁴²

Some researchers suggest that the depletion of CoQ10 could account for some side-effects associated with statin drugs, such as myotoxicity and hepatotoxicity.^{43,44} It has also been hypothesized that the relatively common side-effects of fatigue and rhabdomyolysis may be associated to some degree with CoQ10 status.

Antihypertensives

Common antihypertensive medications include beta-adrenergic blockers, calcium-channel blockers, angiotensin-converting enzyme (ACE) inhibitors, diuretics, and vasodilators. According to the American Heart Association, an estimated 65 million Americans, almost 1 in 3 adults, has high blood pressure.⁴⁵

Vasodilators such as hydralazine deplete vitamin B₆.⁴⁶ Captopril, an ACE inhibitor, has been shown to cause hyponatremia by increasing sodium excretion and may cause hyperkalemia.^{47,48} In addition, studies with the beta blocker propranolol have shown that the drug inhibits the CoQ10 enzymes in the myocardium.⁴⁹

Clinically, it is imperative to control for potential overt and subclinical deficiency states that may otherwise spur the progression of the disease state being treated, or that may manifest

with new adverse biochemical imbalances that may otherwise ripple through the 50 trillion-plus cells that comprise the human frame.

Diuretics

Diuretics are known for altering certain nutrient levels such as potassium; however, many other nutrients are affected. Thiazide diuretics have been shown to deplete magnesium, sodium, potassium, and zinc. One study found hyponatremia in 13.7 percent of individuals treated with thiazide diuretics and hypokalemia in 8.5 percent of these individuals.⁵⁰ Thiazide diuretics also decrease magnesium in approximately 20 percent of patients.⁵¹ In addition, research indicates that thiazide diuretics cause significantly decreased serum zinc.⁵²

Loop diuretics have been shown to deplete potassium, magnesium, calcium, zinc, pyridoxine, thiamine, and ascorbic acid. One study showed that thiamine deficiency was found in 98 percent of patients with congestive heart failure who took 80 mg of furosemide daily and in 57 percent of such patients who took 40 mg daily.⁵³ Ascorbic acid and pyridoxine excretion are also increased with furosemide treatment.⁵⁴

In addition, several studies demonstrate that loop diuretics increase the excretion of sodium, potassium, calcium, magnesium, and chloride.⁵⁵ Although there is a lack of evidence for other nutrient depletions relative to diuretics, the astute clinician will be watchful for one or more water-soluble vitamin, mineral, and accessory nutrient depletions, including other members of the B vitamin family and substances such as L-carnitine.

Anticonvulsants

According to the CDC, epilepsy affects 2.7 million Americans.⁵⁶ Anticonvulsants are commonly used to treat seizure disorders, but are also occasionally prescribed for patients who have anxiety, chronic pain, or migraine headaches.^{57,58}

Several classes of anticonvulsants have been shown to affect nutrient metabolism. Barbiturates have been well-documented to interact adversely with several nutrients and cause osteomalacia. Hypocalcemia and decreased serum 25-hydroxy-vitamin D has been documented in patients treated with phenytoin and phenobarbitone. This study showed that approximately 11 percent of these individuals were deficient in vitamin D, and supraphysiologic doses of vitamin D were required to restore their calcium levels to normal.⁵⁹

One study showed that 29 percent of patients treated with phenobarbital or phenytoin were hypocalcemic.⁶⁰ In addition, studies indicate that these drugs do not affect absorption of folic acid, yet all of the patients who were taking anticonvulsants had reduced serum folate.⁶¹ However, research has also shown that folate supplementation in large doses for patients with epilepsy who are on anticonvulsant therapy can induce seizure activity, thus, caution is advised.⁶²

Several anticonvulsants, such as carbamazepine, phenytoin, and phenobarbital, have been reported to decrease biotin in long-term therapy, possibly by increasing biotin catabolism and excretion.⁶³ Thiamine has been found to be low in both the cerebrospinal fluid and blood in patients with epilepsy who take phenytoin.⁶⁴

Symptoms of Nutrient Deficiency

Nutrients	Symptoms
Thiamine	Beriberi, depression, memory loss, numbness, fatigue
Riboflavin	Cheilosis, glossitis, dermatitis, visual disturbance
Niacin	Pellegra, dermatitis, confusion, diarrhea
Pantothenic acid	Fatigue, numbness and pain in the feet
Pyridoxine	Depression, fatigue, dermatitis, anemia, glucose intolerance
Cobalamin	Anemia, fatigue, poor nerve function, diarrhea
Folate	Anemia, fatigue, cervical dysplasia, diarrhea, gingivitis, depression, irritability, insomnia
Biotin	Alopecia, depression, dermatitis, nausea, anorexia
Vitamin C	Scurvy, decreased immunity, poor wound healing
Calcium	Rickets, osteoporosis, osteomalacia, muscle spasms
Magnesium	Fatigue, irritability, weakness, muscle cramps, insomnia, anorexia, poor nerve conduction
Potassium	Fatigue, irregular heart beat, irritability, confusion, poor nerve conduction
Iron	Anemia, weakness, fatigue, poor immune function
Zinc	Slow wound healing, decreased immunity, loss of taste and smell, alopecia, skin disorders
Selenium	Keshan disease, poor immune function
CoQ10	Hypertension, fatigue, cardiovascular diseases
L-Carnitine	Muscle weakness, poor lipid metabolism, failure to thrive in children

From ref. 75.

CoQ10 = coenzyme Q10.

Pharmaceuticals and Nutrient Depletion

Pharmaceuticals	Nutrients depleted
Estrogen/progestins	Riboflavin, pyridoxine, cobalamin, folic acid, ascorbic acid, zinc, magnesium
Statins	CoQ10
Acid blockers	CoQ10, cobalamin, folic acid, iron, vitamin D, beta-carotene, zinc
Corticosteroids	Calcium, magnesium, potassium, zinc, copper selenium, ascorbic acid, vitamin D
Aspirin	Ascorbic acid, iron, folic acid
Antidiabetes drugs	Cobalamin, folic acid, CoQ10
Anticonvulsants	Biotin, thiamine, cobalamin, folic acid, CoQ10, vitamin D, vitamin K, calcium, L-carnitine
Antihypertensives	Pyridoxine, sodium, CoQ10
Diuretics	Thiamine, pyridoxine, ascorbic acid, potassium, magnesium, calcium, zinc, sodium
Antibiotics	B vitamins, vitamin K, magnesium, calcium potassium, zinc, iron

CoQ10 = coenzyme Q10.

Research results are conflicting regarding vitamin K and anti-convulsant therapy, yet some researchers and animal studies suggest that phenytoin and phenobarbital do alter vitamin K metabolism.^{65,66}

Several studies have shown that valproate, more commonly known as Depakote, causes a decrease in serum free L-carnitine. One study showed that 76.5 percent of adult patients treated with valproate were deficient in serum free L-carnitine and 21.5 percent of individuals treated with other anticonvulsants were also deficient in L-carnitine.⁶⁷ In the case of valproate therapy many physicians are now routinely prescribing L-carnitine proactively to lessen the side-effect profile in these patients.

Antibiotics

Several classes of antibiotics have been shown to affect vitamin and mineral levels. Aminoglycosides are prescribed to 3.2 million patients in the United States annually.⁶⁸ Aminoglycosides such as gentamicin have been shown to cause imbalances of magnesium, calcium, and potassium.⁶⁹

One study showed that gentamicin causes increased excretion of calcium by 5 percent and magnesium by 8.4 percent.⁷⁰ Tetracycline has been shown to bind with multivalent cations, such as aluminum, calcium, magnesium, zinc, and iron, in the gastrointestinal (GI) tract. This binding forms complexes that are absorbed poorly or are insoluble.^{71,72}

Broad-spectrum antibiotics disrupt the normal and beneficial intestinal flora.⁷³ These bacteria are necessary for the synthesis of both B vitamins and vitamin K along with other nutrients, although there are no current studies determining the effects of antibiotics on these vitamin levels.⁷⁴ This interaction could potentially affect these nutrient levels. Strangely enough, though the medical literature abounds with evidence on the use of probiotics such as *Lactobacillus GG* and others to avert antibiotic diarrhea and secondary GI infections, the practice of supplementation on a routine basis is not yet a standard of practice.

Common Nutrients Depleted by Pharmaceuticals

The potential biochemical consequences and resulting imbalances that could otherwise be preemptively guarded against are described briefly in the sections below.

Thiamine

Thiamine (vitamin B₁) is a coenzyme essential for energy metabolism, particularly for carbohydrate metabolism in the brain. The vitamin is also required for synthesis of the neurotransmitter acetylcholine.⁷⁵ Anticonvulsants and diuretics may deplete thiamine.⁷⁶

Riboflavin

Riboflavin (vitamin B₂) is incorporated into the coenzymes FNM and FAD, which are required for cellular energy production. The vitamin is also involved with pyridoxine activation; conversion of folate to coenzymes and tryptophan to niacin; and glucose metabolism.⁷⁷ Drugs associated with depletion of riboflavin include thiazide diuretics, tetracycline, sulfonamides, birth control pills, antimalarials, and probenecid.^{75,77} Tricyclic antidepressants and the antipsychotic drug chlorpromazine also may cause a deficiency.⁷⁶

Niacin

Niacin (vitamin B₃) is integrated into the coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP), which are necessary for amino-acid, fat, and carbohydrate metabolism, producing cellular energy. Niacin supplementation is often used to address hypercholesterolemia and as an anxiolytic.⁷⁷ Isoniazid for treating tuberculosis has been shown to inhibit the conversion of tryptophan to niacin and may cause pellagra.⁷⁸

Pyridoxine

Pyridoxine (vitamin B₆) is an enzymatic cofactor required for synthesis of tryptophan, serotonin, gamma aminobutyric acid (GABA), acetylcholine, histamine, and norepinephrine. The vita-

min is also important in the metabolism of homocysteine. In addition, pyridoxine is involved in hemoglobin synthesis and energy production. Drugs that affect pyridoxine levels adversely include isoniazid, birth control pills and other oral estrogens, penicillamine, hydralazine, and levodopa.⁷⁶ Loop diuretics also deplete pyridoxine.⁵⁴

Cobalamin

Cobalamin (vitamin B₁₂) is a methyl donor and is required for proper DNA synthesis. This vitamin is involved with carbohydrate metabolism and is required for myelin synthesis. Cobalamin also is necessary to convert homocysteine to methionine. Drugs that interfere with cobalamin include oral contraceptives, H₂ blockers, PPIs, antibiotics such as tetracycline and neomycin, bile-acid sequestrants such as cholestyramine, and biguanides such as phenformin and metformin.^{37,76}

Folate

Folic acid is required for DNA synthesis and cellular division. It is also necessary for neural development and cancer prevention. Folic-acid deficiency in pregnancy is linked to multiple birth defects such as neural-tube defects. Folate is also required to convert homocysteine to methionine, thus making this nutrient important in cardiovascular disease prevention. Numerous drugs affect folate levels and metabolism. Some of these drugs include estrogens, anticonvulsants, barbiturates, sulfasalazine, and methotrexate.⁷⁵ Acid blockers, aspirin, cholestyramine, corticosteroids, and the antibiotic trimethoprim also may decrease folic acid.⁷⁶

Biotin

Biotin is a cofactor for several enzymes involved in carbohydrate, amino acid, and fat metabolism. This nutrient is also involved with glucose utilization. Biotin is produced by normal intestinal flora; therefore antibiotics may decrease biotin levels.⁷⁵ Anticonvulsants, such as phenytoin, phenobarbital, and carbamazepine, deplete biotin.⁶³

Ascorbic Acid

Ascorbic acid (vitamin C) is required for numerous physiologic functions. It is required for collagen synthesis and proper immune function and acts as a potent antioxidant and antihistamine. Vitamin C is a cofactor for the enzyme that converts tyrosine to norepinephrine and increases absorption of iron from the small intestines when taken concurrently.⁷⁷ Ascorbic acid may be depleted by corticosteroids, diuretics, aspirin, and estrogens.^{9,54,76}

Vitamin D

Vitamin D is vital for proper calcium metabolism and cancer prevention.* Drugs that may affect vitamin D include acid blockers, corticosteroids, and anticonvulsants.⁷⁶

Vitamin K

Vitamin K is required for synthesizing clotting factors. It also is important for activating osteocalcin, a protein in bone that maintains calcium in the bone. Vitamin K₂, or menaquinone, is made by intestinal flora and may be disrupted by antibiotic use.⁷⁴ Anticonvulsants may also affect vitamin K levels adversely.⁷⁶

Calcium

Calcium is necessary for numerous physiologic functions. It is important for bone and teeth integrity and for blood clotting, muscle contraction, and neurotransmitter regulation. Drugs that interfere with calcium include corticosteroids, anticonvulsants, antibiotics such as tetracycline and aminoglycosides, loop diuretics, methotrexate, and isoniazid.⁷⁶

Magnesium

Magnesium is essential for normal heart contractility and relaxes smooth muscle. This mineral also is required for proper calcium balance and bone and teeth integrity. Magnesium also acts as a calcium-channel blocker, possibly decreasing blood pressure and improving cardiac function. Drugs that affect magnesium include diuretics, corticosteroids, antibiotics, cyclosporine, and chemotherapeutic drugs.⁷⁷

Potassium

Potassium is required for intracellular water balance as well as acid-base balance. This mineral converts glucose into glycogen for storage and is required for nerve conduction and muscle contraction. Potassium is depleted by diuretics, tetracycline, aminoglycoside antibiotics, and aspirin.⁷⁶

Iron

Iron is a component of heme, which comprises hemoglobin and myoglobin. These are necessary for oxygen transport. Pharmaceuticals that may induce iron deficiency include aspirin, acid blockers, thyroxine, and quinolone antibiotics.⁷⁶

Zinc

Zinc is required for numerous physiologic functions. It is involved with proper immune function, hormone production, taste perception, wound healing, prostate function, and vision. Zinc may be depleted by acid blockers, birth-control pills, zidovudine (AZT), and diuretics.^{9,76}

Selenium

Selenium is important for detoxification reactions and for converting thyroxine to the more active form tri-iodothyronine. Corticosteroids have been shown to deplete selenium.²⁸

Coenzyme Q10

CoQ10 is a potent antioxidant protecting against lipid peroxidation as well as being necessary for energy production in the mitochondria. Statin drugs inhibit synthesis of CoQ10 by inhibiting the enzyme HMG CoA reductase. Beta blockers, tricyclic antidepressants, and phenothiazine may also alter CoQ10 function.⁷⁵

*EDITOR'S NOTE: There is some controversy about whether or not vitamin D has an anticancer effect.

L-Carnitine

L-Carnitine is a nonessential amino acid synthesized from lysine and methionine. It regulates energy production in muscle tissue and is particularly important for cardiac function. Carnitine is also involved with fat metabolism as well as using amino acids for energy. Anticonvulsants such as valproate have been shown to deplete carnitine significantly.⁷⁹ AZT also depletes carnitine.⁸⁰

Conclusions

Pharmaceutical-induced nutrient deficiency may be more common than most health care providers currently acknowledge. Patients who are most at risk for drug-induced deficiencies may be individuals who have borderline nutritional status or poor dietary intake of nutrients. It is hoped that new support of vitamin and mineral supplementation on the part of clinicians will encourage patients to optimize their nutritional status and decrease the risk of nutrient deficiencies. □

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