Drug-Induced Nutrient Depletion

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Lesson description

Pharmacists are challenged on a daily basis with assessing the appropriateness of medication for a patient's particular circumstances. Assessing the appropriateness of medication with regard to the implications of drug-induced nutrient depletion may not always be top of mind for health professionals. This continuing education lesson has been created with the goal of helping pharmacists take a systematic approach to assessing the potential for drug-induced nutrient depletion. Strategies for prevention and treatment of common drug-induced nutrient depletion consequences are also presented.

Learning objectives

After completing this continuing education module, pharmacists will be better able to:

- discuss several mechanisms of drug-induced nutrient depletion
- identify medications most commonly associated with drug-induced nutrient depletion
- assess the clinical significance of potential drug-induced nutrient depletion circumstances
- recommend prevention and treatment strategies for management of drug-induced nutrient depletion

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1. Introduction

1.1 Background

Pharmacists are challenged on a daily basis with assessing the appropriateness of medication for a patient's individual circumstances. Assessing the appropriateness of medication with regard to the implications of drug-induced nutrient depletion may pose a particular challenge. This continuing education lesson has been created with the goal of helping you take a systematic approach to assessing the potential for drug-induced nutrient depletion.

Many of today's commonly prescribed and over-the-counter medications can contribute to nutritional deficiencies through various mechanisms. One author asserts that over 1,000 medications, including 15 of the top 20 most prescribed drugs, cause nutrient depletion.[1] It is important to put this information in perspective, however: many individuals who take medications known to deplete nutrients will not be affected clinically.

Canada has never had a formal, systematic program of national food and nutrition surveillance.[2] In the United States, the results of surveys such as the National Health and Nutrition Examination Survey (NHANES-II) have revealed that 91% of respondents do not eat 3 servings of vegetables and fruits a day, and another from the US Department of Agriculture suggests that 80% of Americans do not consume the recommended dietary allowance (RDA) of one or more of the essential nutrients on a daily basis. Assuming a somewhat similar situation in Canada, these findings suggest that as health professionals we need to assess the patient as a whole when considering their nutritional needs and the potential impact of medications that may cause or exacerbate nutritional deficiencies.

Some commonly prescribed drugs that cause nutrient depletion include antibiotics, oral contraceptives, anticonvulsants, anti-diabetics, antihypertensives, anti-inflammatories, dyslipidemic agents, and acid-reducing agents. One popular brand of nutritional vitamin and mineral supplements manufactured in the United States offers 5 different formulations based on types of medications a person is taking (cholesterol medication, heartburn and acid reflux medication, antidepressant medication, arthritis medication, diabetes medication). The manufacturer claims that "nutrient levels may be reduced for 135 million Americans taking prescription medications."[3] A review of the formulations of these vitamins and minerals described the utility of these supplements as "probably marginal," stating that in most cases people who eat a healthy diet and take a multivitamin (which contains a more complete range of vitamins and minerals) won't need them.[4]

Ensure that your patients understand that nutritional intake, like medications, needs to be tailored to the individual and that if a patient is taking chronic medications a health professional should be consulted before starting anything new. This prevents occurrences such as duplication of intake or unintentional interaction with other medications a patient may be taking.

This continuing education module has been designed to provide an overview of the mechanisms of drug-induced nutrient depletion, a listing of common nutrients affected in a clinically important manner (and associated nutrient-depleting drugs), and the potential clinical consequences of each nutrient depletion. Recommendations for the screening and prevention of these issues are also reviewed. The module has been designed so that it may be used as a tool for quick reference in the pharmacy.

2. Mechanisms of drug-induced nutrient depletion

There are a number of potential mechanisms associated with drug-induced nutrient depletion. The following are some common mechanisms:

- decreased absorption from the gut secondary to chelation and formation of insoluble complexes (e.g., binding of minerals to antacids [aluminum hydroxide])
- decreased absorption from the gut secondary to sequestration or solubility in the lipid phase (e.g., binding of fat-soluble vitamins to cholestyramine, solubility of fat-soluble vitamins in mineral oil)
- decreased release of nutrient from the food matrix secondary to changes in the pH of the stomach (e.g., proton pump inhibitors and absorption efficiency of non-heme iron)
- metabolism of drug decreasing conversion to the active form (e.g., phosphorylation of pyridoxine during treatment with isoniazid, binding to dihydrofolate reductase by methotrexate)
- metabolism of drug increasing degradation of the vitamin (e.g., increase of hepatic metabolism of vitamin D during treatment with some types of anticonvulsants)

For review purposes, this module has been organized according to the nutrient depleted. For an alphabetical listing of drugs and associated risk for nutrient depletion, please refer to Appendix 1.

3. Assessing implications of nutrient depletion

In order to assess the implications of potential drug-induced depletion we first need to understand the nutritional needs of individuals.

3.1 What is a nutrient?

A nutrient is defined as any substance that our body requires in order to survive and thrive. Nutrients found in food are necessary for growth, energy, supplying building materials for our body, and maintaining and repairing our body's tissues.[5]

A healthy body is made up of about 60% water and about 20% fat (lipids). The other 20% is made up mostly of substances containing protein and carbohydrate and the major minerals of the bones. Drug-induced nutrient depletion affects levels of vitamins and minerals and other nutrients (e.g., coenzyme Q_{10}) in the body. Vitamins are vital for life and good health because of their role in aiding the chemical processes that occur as part of the body's metabolism. Minerals occur as atoms of a single element and are found in orderly arrays in such structures as bones and teeth. Minerals can also be found in the fluids of the body (e.g., potassium, chlorine), where they affect fluid and electrolyte balance. Almost all of the body's activities take place in water. They are involved in many of the reactions that occur in metabolism and provide the means for transporting materials to cells and taking waste products away from them.

3.2 Vitamins and minerals (the micronutrients)

There are 13 different vitamins (A, C, D, E, K, and eight different B vitamins), all of which have important roles to play in the body's life-sustaining biochemical processes. Vitamins usually perform hormone-like functions and assist in the protection of cell membranes.[5] Vitamins A, D, E, and K are "fat-soluble" vitamins, while vitamin C and the B vitamins are water-soluble. The solubility of vitamins has implications for drug-induced nutrient depletion. For example, orlistat may cause depletion of fat-soluble vitamins secondary to prevention of breakdown of triglycerides in the intestine. Minerals are naturally occurring inorganic elements that have 3 main roles in the body: structural (e.g., in formation of bones and teeth), functional (e.g., in maintenance of normal heart rhythm, muscular contractility, neural conductivity, and acid-base balance), and regulatory (i.e., in cellular metabolism such as activation of enzymes and hormones).

In 1998 a comprehensive set of reference values for nutrient intakes for healthy North American populations known as Dietary Reference Intakes (DRIs) was published through a partnership between the US Institute of Medicine and Health Canada. A listing of DRIs for micronutrients can be found in Appendices 2 and 3.

4. Nutrients and drug-induced depletion

The following sections do not include all potential nutrient depletions but capture a majority of those that are likely to be depleted by drug ingestion in a clinically significant manner. Nutrients are listed alphabetically. This approach differs from most other approaches to this topic, which list drugs followed by nutrients that they deplete. A chart of this nature for cross-reference can be found in Appendix 1.

4.1 Calcium

Implicated drugs: corticosteroids, loop diuretics, magnesium salts, mineral oil, proton pump inhibitors, stimulant laxatives, tetracycline

4.1.1 Drug-induced mechanisms of depletion and potential clinical consequences

Calcium depletion over the long term can result in loss of bone mineral density and, ultimately, osteoporosis. Long–term **corticosteroid** therapy is by far the most common cause of this outcome. Corticosteroids have been shown to increase renal calcium excretion and decrease intestinal calcium absorption.[6]

Calcium depletion associated with drug intake resulting in hypocalcemia is not common. However, patients with lower calcium levels may be pushed to hypocalcemia by:[6]

- prolonged use of large doses of magnesium salts such as those found in milk of magnesia or antacids (binds calcium and phosphate in the gastrointestinal tract)
- higher doses of loop diuretics (e.g., furosemide, ethacrynic acid, bumetanide) or when used with diuretics of another class (causes increased urinary excretion)
- prolonged use of oral mineral oil (decreases gastrointestinal absorption)
- excessive use of stimulant laxatives (decreases gastrointestinal absorption)
- use of drugs that deplete vitamin D, thereby reducing absorption of calcium (see vitamin D section 4.10.1)

- longer-term tetracycline or fluoroquinolone therapy (these antibiotics may form complexes with calcium in GI tract and prevent absorption)
- a low-gastric-acid environment (associated with chronic proton pump inhibitor use in particular) – low gastric acidity may reduce calcium absorption (especially calcium supplements)[7]

4.1.2 Screening, prevention, and treatment

The Canadian Clinical Practice Guidelines for Osteoporosis list treatment with moderate-to-high-dose (>7.5 mg prednisone or equivalent) systemic corticosteroid therapy for 3 months or longer as a major risk factor for osteoporosis.[8] Pharmacists should routinely inquire about bone mineral density (BMD) testing in patients meeting this criterion, as dual X-ray absorptiometry (DXA) is indicated.[8] In addition, patients should be counselled to ensure they are ingesting sufficient daily calcium and vitamin D to meet the recommendations of the Osteoporosis Society of Canada.[8] Supplementation may be started routinely by some physicians who expect their patients to be using systemic corticosteroid therapy for more than 3 months.

Prolonged administration of large doses of magnesium salts (e.g., milk of magnesia, antacids containing magnesium hydroxide, supplements), mineral oil, and stimulant laxatives should be avoided by patients.[6]

High doses of loop diuretics and/or use with diuretics of a different class can cause increased urinary excretion of a number of calcium as well as other electrolytes (magnesium, potassium, sodium).[6] Referral where patients have not discussed this issue with their prescribing physician is in order, as proactive supplementation may be appropriate in some patients. It should be noted that unlike loop diuretics, thiazide diuretics lower calcium excretion by the kidney.

Patients using tetracycline or fluoroquinolones should be advised to take their antibiotic at least 2 hours before or 4–6 hours after calcium, iron, magnesium, or zinc intake.[9]

Pharmacists should remind patients at risk for osteoporosis who are taking long-term proton pump inhibitor therapy to have bone mineral density tests conducted at appropriate intervals as discussed with their medical practitioner.

Pharmacists should ensure that patients understand that calcium requirements are expressed in terms of elemental calcium. For example, 1,250 mg calcium carbonate contains only 500 mg elemental calcium. The Osteoporosis Society of Canada website offers a "calcium calculator" which can help one to determine one's daily intake of calcium. Recipes high in calcium are also available on the website. Refer to Appendix 3 for Osteoporosis Society of Canada recommendations for daily intake of calcium according to age.

The following are some important counselling points regarding supplementation with calcium:

- All calcium supplements should be taken with plenty of water.
- Calcium should be taken in smaller amounts during the day rather than in a single large dose. Smaller doses (500 mg to 600 mg) are absorbed more easily and more completely. To maximize absorption of calcium supplements, they should not be taken at the same time as a high-calcium meal.
- Patients should be counselled that calcium supplements may cause stomach upset, constipation, or nausea.
- Calcium may interfere with the absorption of other medications; therefore, patients should be asked about other medications they may be taking, including prescription, over-the-counter, and herbals, and should be counselled accordingly. Examples of medications whose absorption is affected by calcium include iron, zinc, atenolol and propranolol (decreased oral bioavailability), salicylates (with chronic administration – reduction in salicylate renal tubular reabsorption due to urinary alkalinization), levothyroxine (reduced oral bioavailability), bisphosphonates, fluoroquinolones, and tetracyclines.[10]
- Calcium salts are contraindicated in people with hyperparathyroidism, vitamin D overdosage, decalcifying tumours such as plasmacytoma, bone metastases, severe cardiac disease, ventricular fibrillation, and calcium loss due to immobilization.
- Calcium salts should be used with caution in patients with renal disease, kidney stones, and sarcoidosis (a chronic disease characterized by nodules in the lungs, skin, lymph nodes, and bones).

4.2 Carnitine

Implicated drugs: valproic acid

4.2.1 Drug-induced mechanisms of depletion and potential clinical consequences

Carnitine is derived from an amino acid and is found in virtually all cells of the body.[11] It helps the body convert fatty acids into energy, which is used primarily for muscular activities throughout the body. The body produces carnitine in the liver and kidneys and stores it in the skeletal muscles, heart, brain, and sperm.[6]

Dietary carnitine is thought to be actively transported across the intestine in a sodium-depend-

ent manner. It is excreted intact by the kidneys either as free carnitine or as acylcarnitine.[12] The concentration of carnitine in the blood is regulated mainly by the kinetics of carnitine reabsorption by the kidney, the proximal renal tubule reabsorbing >90% of filtered carnitine at normal physiologic concentrations.

Valproic acid is the drug most commonly associated with carnitine deficiency. It inhibits the biosynthesis of carnitine and may decrease the tissue uptake of carnitine.

Carnitine deficiency (most common with use of valproic acid) may be associated with anemia, fatigue, increased blood levels of ammonia, lethargy, unexplained stupor, and cardiac irregularities.[13] There is a high incidence of hepatotoxicity associated with carnitine deficiency, especially in infants and young children using valproic acid.[12] The deficiency is most likely due to drug-induced aggravation of acquired nutritional issues.

4.2.2 Screening, prevention, and treatment

Any patients with primary plasmalemmal carnitine transporter defect (a genetic disorder identified with genetic testing) should take oral L-carnitine supplementation.[6]

In addition, for special subgroups of patients taking valproic acid, oral L-carnitine supplementation should be considered. These include:[6]

- patients with valproic-acid-associated hyperammonemia
- patients with multiple risk factors for valproic-acid-associated hepatotoxicity, or renal associated syndromes
- infants and young children taking valproic acid
- patients with epilepsy using the ketogenic diet that may have hypocarnitinemia
- patients on dialysis
- premature infants receiving total parenteral nutrition

An oral L-carnitine dose of 100 mg/kg/day, up to a maximum of 2 g/day, has been recommended for supplementation.

4.3 Coenzyme Q_{10}

Implicated drugs: statins

4.3.1 Drug-induced mechanisms of depletion and potential clinical consequences

Coenzyme Q_{10} is an essential cofactor in the mitochondrial electron transport pathway and is a lipid-soluble antioxidant.[14] It is synthesized via the mevalonate pathway.[14] Statins, which are 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors, block the synthesis of mevalonic acid, which is a precursor of coenzyme Q_{10}.[14] Many studies have demonstrated reductions of up to 54% in plasma/serum coenzyme Q_{10} levels following statin therapy.[14]

Coenzyme Q_{10} deficiency has been postulated to be associated with statin-induced myopathy, aggravation of heart failure symptoms, endothelial dysfunction leading to impaired beta-cell function and increased risk for diabetes, and aggravation of Parkinson's disease symptoms.[14] All of these hypothesized effects of coenzyme Q_{10} depletion are deemed to be associated with mechanisms of mitochondrial electron transport and ATP synthesis and/or oxidative stress pathophysiologies.[14]

Circulating concentrations of coenzyme Q_{10} do not necessarily reflect tissue levels. This may explain the challenges that have been associated in linking coenzyme Q_{10} supplementation with benefit associated with reducing adverse effects of myopathy caused by statin therapy (see below).[6]

4.3.2. Screening, prevention, and treatment

Coenzyme Q_{10} supplementation for patients taking statins has become very popular in recent years based on the assumption that reduced levels of the factor are associated with increased adverse outcomes related to the drugs.

Only two randomized trials to date have assessed the effect of coenzyme Q_{10} supplementation on statin-induced myalgia:

- In the first study, Caso and colleagues reported a 40% reduction in myopathic pain ($p<0.001$) after 30 days of coenzyme Q_{10} 100 mg/day versus vitamin E 400 IU per day.[15] However, the study included only 32 patients, it was not placebo controlled (vitamin E has not previously been shown to reduce myopathy), and statin dose was not standardized.
- In the second study, Young and colleagues randomized 44 patients with prior statin-induced myalgia to treatment with 200 mg/ day coenzyme Q_{10} or placebo for 12 weeks in combination with upward dose titration of simvastatin at 10 mg/day, doubling every 4 weeks if tolerated to a maximum of 40 mg/day.[16] There were no significant differences in myalgia score change, or differences in patients tolerating statins between the two treatment groups.

It is evident that adequately powered randomized controlled trials are required to establish the role of coenzyme Q_{10} supplementation in management of statin-induced myopathy.[14] If, after explanation of current levels of evidence, patients wish to use coenzyme Q_{10} supplementation, they can be assured that there have been few reports of adverse

effects. Gastrointestinal side effects such as nausea, vomiting, diarrhea, appetite suppression, heartburn, and epigastric discomfort have been reported in less than 1% of patients.[9] The most common doses used are 100–200 mg daily.[9]

4.4 Folic acid

Implicated drugs: anticonvulsants (carbamazepine, phenytoin, phenobarbital), estrogens, estrogen-containing oral contraceptives, methotrexate, triamterene, trimethoprim

4.4.1 Drug-induced mechanisms of depletion and potential clinical consequences

Folic acid is a B vitamin important for the synthesis, repair, and functioning of DNA.[17] It is also important for the production and maintenance of new cells. It is especially important during periods of rapid cell division and growth that occurs during pregnancy and in the development of young children.[17]

Folic acid may be depleted by induction of hepatic microsomal enzymes and/or decreased intestinal absorption (anticonvulsants). Methotrexate and trimethoprim as well as, to a lesser extent, triamterene can cause folate antagonism by binding to dihydrofolate reductase.[6]

The following are potential medical problems arising from folate deficiency:[18]

- increased risk for infants with low birth weight, premature birth, and/or neural tube defects
- megaloblastic anemia (along with deficiency in vitamin B_{12}) – symptoms consistent with anemia such as loss of appetite, pale skin colour, fatigue, and tingling and numbness in hands and feet[19]
- slow overall growth rate in children
- increased homocysteine blood levels
- aggravation of methotrexate-related toxicities such as mucositis, mild alopecia, and GI disturbances[6]

4.4.2 Screening, prevention, and treatment

It is common knowledge that virtually all pregnant women should take a folic acid supplement regardless of medications being taken. Typically, researchers recommend an intake of synthetic folic acid 400 µg daily from fortified foods and/or dietary supplements.[20] The dose of folic acid taken by a pregnant woman taking medication that could potentially further deplete the vitamin should be individualized for the patient by her physician. Folic acid supplementation should be recommended in collaboration with the patient's physician, naturopathic doctor, or other qualified health professional for those receiving methotrexate for psoriasis, rheumatoid arthritis, and other indications requiring prolonged therapy with methotrexate. Folic acid at a dose of 1 mg daily (5–7 mg once a week) is less expensive and less complicated than use of folinic acid. At these low doses, folic acid does not interfere with the beneficial effects of methotrexate.[6,21]

Some recommend giving folic acid supplementation with the initial dose of phenytoin to prevent deficiency. It should be noted that folic acid supplementation may alter phenytoin pharmacokinetics, leading to lower serum concentrations and possible seizure breakthrough.[22] Therefore, folic acid therapy should be initiated only in collaboration with a physician. Supplementation with folic acid for patients with long-term use of carbamazepine, phenobarbital, triamterene, or trimethoprim has not been studied.[6]

Folic acid supplements should be considered when taking estrogen-containing products only where low dietary intake exists, or with other conditions that contribute to folate deficiency.[9]

4.5 Iron

Implicated drugs: acid suppressant therapies, fluoroquinolones, nonsteroidal anti-inflammatory drugs, salicylates, tetracyclines

4.5.1 Drug-induced mechanisms of depletion and potential clinical consequences

Iron deficiency causes symptoms of anemia such as fatigue, pallor, brittle nails, palpitations, weakness, shortness of breath, sore tongue, and headache.[23]

Gastrointestinal-acid-suppressing agents (antacids, H_2-antagonists, proton pump inhibitors) may reduce iron levels by reducing absorption of dietary, non-heme iron. Non-heme iron (60% of iron found in animal tissue and 100% of iron found in fruits and vegetables) is less easily absorbed than heme iron. Anemia is unlikely in people with normal iron stores, but iron supplementation may be necessary in people with other contributing factors.[9]

Nonsteroidal anti-inflammatory drugs and salicylates can cause iron deficiency through mucosal damage and gastrointestinal bleeding. This may occur asymptomatically in some individuals.[9]

Fluoroquinolones and tetracycline may form insoluble complexes with iron, preventing its absorption.

4.5.2 Screening, prevention, and treatment

Patients using the medications described above should be encouraged to maintain adequate dietary intake of iron and should be assessed for additional risk factors for iron depletion (e.g., low iron intake, pregnancy, heavy menstrual periods, blood loss). Where necessary, patients should be referred to their physician for further assessment.

In people where iron supplementation is necessary, it is important to understand the differences between the various iron salts and products. Iron supplements are most often provided as either ferrous fumarate (33% elemental iron), ferrous sulfate (20% elemental iron), or ferrous gluconate (12% elemental iron). The percentage of iron absorbed decreases with increasing doses. Therefore, iron supplements should be taken in 2 or 3 daily doses. Iron deficiency anemia is often treated with 50–60 mg oral elemental iron twice daily for 3 months.[24]

Iron levels are monitored by measuring hemoglobin levels, ferritin levels, and reticulocyte counts (levels of newly formed red blood cells). Reticulocyte counts usually begin to rise within a few days of supplementation, while hemoglobin differences are usually apparent within 2 to 3 weeks.[24]

Iron can accumulate in body tissues and organs if storage sites are full. Iron overload results in iron being stored in organs such as the liver and heart, causing damage such as cirrhosis of the liver and heart failure.[24] Children are especially at risk for acute iron toxicity, and death has occurred from ingesting as little as 200 mg of iron. Therefore, all patients should be warned to keep iron supplements tightly capped and away from children.[24]

4.6 Magnesium

Implicated drugs: aminoglycosides, amphotericin b, cisplatin, cyclosporine, pentamidine, digoxin, loop diuretics, thiazide diuretics, sodium phosphates, estrogens, fluoroquinolones, tetracyclines

4.6.1 Drug-induced mechanisms of depletion and potential clinical consequences

Magnesium is an important electrolyte in a large number of cellular metabolic reactions.[25] These include DNA and protein synthesis, neurotransmission, and hormone-receptor binding. It is a component of guanosine triphosphate hydrolase (GTPase) and a cofactor for Na^+/K^+–ATPase, adenylate cyclase, and phosphofructokinase. Magnesium is necessary for the production of parathyroid hormone.[25]

Hypomagnesemia may cause weakness, muscle cramping, and rapid pulse.[25] Altered mental status may be present in severe cases. In less severe cases vertigo, ataxia, depression, and seizure activity may occur.[25] In combination with digoxin, low magnesium levels can increase risk of arrhythmia.

Aminoglycosides, amphotericin b, cisplatin, cyclosporine, and pentamidine cause increased urinary excretion of magnesium, which is likely associated with renal damage.[9] Digoxin causes reduced reabsorption of magnesium in the renal tubule, which leads to excess magnesium excretion.[9] Loop diuretics and thiazide diuretics in higher doses alone or in combination may increase urinary excretion of magnesium.[9] Estrogens may cause a shift of magnesium from plasma to tissues. Sodium phosphates used for preoperative bowel cleansing can cause severe electrolyte disturbances in certain individuals (e.g., elderly and those with other risk factors). Fluoroquinolones and tetracyclines may cause formation of insoluble complexes which prevent absorption of both nutrient and drug.

4.6.2 Screening, prevention, and treatment

Patients using aminoglycosides, amphotericin b, cisplatin, cyclosporine, or pentamidine should be closely monitored for electrolyte disturbances and declining renal function using the RBC magnesium blood test. Intravenous electrolyte replacement (or oral magnesium therapy in some cases) should be instituted if necessary along with consideration of reducing or discontinuing drug where appropriate.[9]

Arrhythmias associated with hypomagnesemia and digoxin use are more likely to occur with concurrent diuretic use.[26] Magnesium levels should be monitored along with digoxin levels and magnesium should be supplemented if warranted.[26]

Loop diuretics and thiazide diuretics are more likely to cause electrolyte disturbances at higher doses and when in combination. Magnesium supplements may be required. Potassium-sparing diuretics may also be used, as these also spare magnesium.[27]

For women taking estrogens, magnesium levels should be monitored for those with additional risk factors for hypomagnesemia and supplemented if necessary.

High doses of sodium phosphates for bowel cleansing should be avoided and electrolyte levels monitored in the elderly and others with risk factors for hypomagnesemia.

Patients using tetracycline or fluoroquinolones should be advised to take their antibiotic at least 2 hours before or 4–6 hours after magnesium (or calcium, iron, magnesium, or zinc) intake.[9]

4.7 Potassium

Implicated drugs: Aminoglycosides, amphotericin b, corticosteroids, diuretics (potassium depleting), penicillins (sodium-containing – carbenicillin, mezlocillin, piperacillin, ticarcillin), stimulant laxatives, theophylline

4.7.1 Drug-induced mechanisms of depletion and potential clinical consequences

Potassium is an extremely important electrolyte in the body. Nearly 98% of the body's potassium is

intracellular.[28] The ratio of intracellular to extracellular potassium is critical for determining the cellular membrane potential. Small changes in extracellular potassium levels can have profound effects on the function of the cardiovascular and neuromuscular systems. The kidney is responsible for potassium homeostasis, and excess potassium is excreted in the urine.[28] Normal potassium levels are considered to be 3.5–5 mmol/L (<3.5 mmol/L potassium is considered hypokalemia).

Symptoms of hypokalemia include skeletal muscle weakness or cramping, paralysis, paresthesias, constipation, nausea or vomiting, abdominal cramping, polyuria, nocturia, polydipsia, psychosis, delirium, hallucinations, and depression. Hypokalemia increases risk for hypotension, arrhythmias, and cardiac arrest.

Aminoglycosides and amphotericin b cause increased urinary excretion of potassium secondary to drug-induced renal damage.

Corticosteroids can cause sodium retention, which results in compensatory renal potassium excretion. This activity is more common with steroids having high mineralocorticoid activity (hydrocortisone, cortisone, fludrocortisones, prednisone, prednisolone).

Potassium-depleting loop and thiazide diuretics enhance renal excretion of potassium.

Sodium-containing penicillins present a large sodium load to the kidneys, resulting in sodium reabsorption and potassium excretion.

Excess use of stimulant laxatives can cause increased intestinal losses of potassium.

Theophylline in high doses (generally greater than 20 µg/mL serum theophylline concentration) may cause increased intracellular uptake of potassium and resultant hypokalemia.[29] Risk for hypokalemia is dose-dependent.

4.7.2 Screening, prevention, and treatment

Potassium should be screened routinely in patients at risk for electrolyte disturbances, such as any patients using any of the drugs listed above.

Patients experiencing hypokalemia while using a corticosteroid with high mineralocorticoid activity can be switched to one with low mineralocorticoid activity (i.e., betamethasone, dexamethasone, methylprednisolone, triamcinolone).[30]

Patients using potassium-depleting diuretics can be given potassium supplements if necessary, or a potassium-sparing diuretic can be added to therapy.

Those using sodium-containing penicillins can be switched to a different antibiotic if necessary.

Stimulant laxative use should be limited to short-term.

Potassium should be monitored closely with higher doses of theophylline therapy, with supplementation if appropriate.

4.8 Pyridoxine

Implicated drugs: isoniazid, hydralazine, penicillamine, estrogens, estrogen-containing oral contraceptives, theophylline

4.8.1 Drug-induced mechanisms of depletion and potential clinical consequences

Pyridoxine (also known as vitamin B_6) is an essential cofactor in various metabolic pathways involving carbohydrates, sphingolipids (a type of lipid occurring in high quantities in the brain and other nerve tissue), sulphur-containing amino acids, heme, and neurotransmitters.[31] It is also a coenzyme of both tryptophan and methionine metabolism. Tryptophan is a precursor to several neurotransmitters and is required for niacin production. Pyridoxine deficiency therefore can cause pellagra (caused by niacin depletion). The neurotransmitters dopamine, serotonin, epinephrine, norepinephrine, glycine, glutamate, and gamma aminobutyric acid (GABA) also require pyridoxine for their production. Homocysteine metabolism is dependent on pyridoxine, and high homocysteine levels can result from pyridoxine deficiency.[31]

Pyridoxine deficiency is rare in healthy individuals.[31] Potential symptoms associated with low pyridoxine levels include weakness, dizziness, inflammation, atherosclerosis, anemia, bilateral distal limb numbness, depression, irritability, confusion, generalized seizures, anorexia, vomiting, and erythematous itching and burning.[31]

Isoniazid interacts with pyridoxine to form an inactive hydrazone which inhibits pyridoxal kinase (required to create the active form of pyridoxine) and increases pyridoxine excretion in the urine.[32] This can cause peripheral neuritis. It is rare in people taking less than 5 mg/kg/day of the drug. Hydralazine and penicillamine may also cause pyridoxine depletion by this mechanism.[33]

Estrogens and estrogen-containing oral contraceptives can interfere with pyridoxine metabolism. Pyridoxine levels seem to correct themselves with use of low-dose estrogen contraceptives.[34]

Theophylline inhibits the enzyme pyridoxal kinase, preventing the metabolism of pyridoxine to its active form.[35] The clinical significance of pyridoxine depletion is not clear, but it has been theorized that pyridoxine deficiency contributes to neurological and CNS side effects, including seizures.[35]

4.8.2 Screening, prevention, and treatment

Patients taking isoniazid in doses of more than 5 mg/kg/day should consider pyridoxine supple-

ments of 50–150 mg daily. All patients should be made aware of the potential and monitored for early signs of peripheral neuropathy such as paresthesias, numbness, and tingling and given pyridoxine if symptoms occur.[33]

Patients taking pencillamine for treatment of Wilson's disease should take pyridoxine 25 mg daily.[33] Supplements of 50–150 mg per day have been used when penicillamine is used for treatment of other conditions. Symptoms of pyridoxine deficiency are not as common with hydralazine treatment but, as for other drugs potentiating pyridoxine deficiency, patients should be made aware of the potential and monitored for early signs of peripheral neuropathy such as paresthesias, numbness, and tingling and given pyridoxine if symptoms occur.[33]

Reports suggest that low pyridoxine levels contribute to the depression, lethargy, and fatigue that is sometimes associated with oral contraceptives. However, there is little evidence to support use of pyridoxine supplements to prevent or treat the symptoms.[33]

Pyridoxine supplements in doses of 10–300 mg daily have been used in people taking theophylline, but results are conflicting. If symptoms as described earlier do occur, then pyridoxine should be offered.[33]

4.9 Vitamin B_{12}

Implicated drugs: acid-reducing agents (antacids, H_2-antagonists, PPIs), aminosalicylic acid, antibiotics, colchicine, cholestyramine and colestipol, metformin, phenytoin, phenobarbital and primidone

4.9.1 Drug-induced mechanisms of depletion and potential clinical consequences

Vitamin B_{12} plays an important role in neurologic function and DNA synthesis.[36] Early identification of symptoms and prompt treatment can reverse many of the hematologic and neuropsychiatric disorders associated with the deficiency.

Symptoms of vitamin B_{12} deficiency may be:

- neurologic – paresthesias, peripheral neuropathy
- psychiatric – irritability, personality change, mild memory impairment, dementia, depression, psychosis
- hematologic – megaloblastic anemia, pancytopenia (leucopenia, thrombocytopenia)

Vitamin B_{12} requires intrinsic factor (synthesized in the gut) for transport into the small intestine and eventual absorption into the blood stream. Deficiency is usually caused by either lack of intrinsic factor or lack of hydrochloric acid required to liberate the vitamin from its protein-bound state (as found in food).[37]

Although acid-reducing agents such as antacids, H_2-antagonists, and proton pump inhibitors have theoretic potential to reduce absorption of vitamin B_{12} by reducing available hydrochloric acid, this activity is unlikely clinically significant.[37]

Aminosalicylic acid has been reported to reduce oral vitamin B_{12} absorption by as much as 55% as part of a general malabsorption syndrome.[38]

Antibiotics may cause disruption of the normal gastrointestinal flora, which can interrupt enterohepatic recirculation of vitamin B_{12} and increase excretion via the feces. However, this is a theoretical issue and unlikely to have clinically significant effects on vitamin B_{12} levels.[38]

Colchicine at doses of 1.9–3.9 mg/day may cause disruption of normal intestinal mucosal function, leading to malabsorption of vitamin B_{12} and other nutrients.[38]

Cholestyramine and colestipol can bind intrinsic factor and vitamin B_{12}–intrinsic factor complexes. However, absorption is not completely prevented and routine supplements aren't normally required.[38]

Metformin is theorized to reduce vitamin B_{12} level by decreasing intrinsic factor secretion, reducing uptake of vitamin B_{12}-intrinsic factor complexes. Reductions in vitamin B_{12} occur in up to 20% of people taking metformin on a chronic basis. If dietary intake of vitamin B_{12} is adequate, clinically significant deficiency isn't likely.[39] Risk factors for metformin-induced B_{12} deficiency include older age, vegetarian diet, higher metformin dose, and use of metformin for 3 years or more.[39]

Phenytoin, phenobarbital, and primidone may reduce vitamin B_{12} absorption, leading to reduced serum and cerebrospinal fluid levels in some patients. It is thought that this may play a role in the megaloblastic anemia, primarily caused by folate deficiency, associated with these drugs.[40]

4.9.2 Screening, prevention, and treatment

For people with risk factors for vitamin B_{12} deficiency (older age, vegetarian diet) and taking any of the medications listed, vitamin B_{12} levels should be monitored regularly. All patients should be urged to include adequate amounts of vitamin B_{12} in their diet (see Appendix 2).

For people taking aminosalicylic acid, symptomatic anemia has occurred after doses of 8–12 g/day for several months.[41] Patients taking this drug for more than one month should be monitored for vitamin B_{12} levels and given supplements if necessary.

For patients taking large doses of colchicine for prolonged periods, vitamin B_{12} should be monitored.[38]

People using chronic metformin therapy should be advised to have their vitamin B_{12} levels checked on an annual basis.

Patients using the anticonvulsant drugs phenytoin, phenobarbital, or primidone should be encouraged to consume adequate amounts of vitamin B_{12} in their diet and have folate and vitamin B_{12} status checked if symptoms of anemia develop (educate patients about the signs of anemia).

Many clinicians assume that oral vitamin B_{12} therapy is not effective and therefore intramuscular injection is necessary for supplementation. However, evidence is mounting to suggest that oral vitamin B_{12} 2,000 µg daily is as effective as vitamin B_{12} given intramuscularly.[42] Evidence also suggests that high doses of oralvitamin B_{12} (1000 µg) initially daily and thereafter weekly and then monthly are as effective as intramuscular vitamin B_{12}, at least in the short term. Research associated with larger populations and longer periods of treatment should be conducted to confirm these findings. Both regimens have been shown safe. It is thought that the oral regimen utilizes a transport mechanism other than the one utilizing intrinsic factor, and that it is effective enough for absorption when the vitamin is taken in these high doses.[36]

4.10 Vitamin D

Implicated drugs: anticonvulsants (carbamazepine, phenoparbital, phenytoin), mineral oil, rifampin, stimulant laxatives, sunscreens

4.10.1 Drug-induced mechanisms of depletion and potential clinical consequences

The major role of vitamin D is to maintain normal plasma levels of calcium and phosphorus. Vitamin D deficiency reduces calcium absorption, which can lead to low bone mineral density (BMD) and ultimately osteoporosis.

Vitamin D is found only in food, but is also synthesized in the skin after the process is triggered by UV rays from the sun. Vitamin D exists in several forms, with calciferol being the most active. Vitamin D must be metabolized by the liver and then the kidneys in order for the most active form to be produced. The active form of vitamin D (1,25-dihydroxycholecalciferol or calcitriol) is synthesized from vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) in the kidney. Vitamin D_2 and vitamin D_3 are the components of most vitamin D supplements. In circumstances where kidney function is impaired (chronic renal failure or dialysis), the active form of the vitamin is used for supplementation.

Dark-skinned people need longer exposure to sunlight to make the same amount of vitamin D as light-skinned people (a ratio of about 3 hours to 30 minutes). For most people, exposing the hands, face, and arms in sunny weather for 10–15 minutes a few times a week provides adequate vitamin D needs.[43] Unfortunately, many people (e.g., housebound individuals, those that wear robes and head coverings for religious reasons) are unable to obtain enough vitamin D from sunlight to meet their requirements.[44]

High caffeine intake may interfere with vitamin D receptors, thereby interfering with the ability of vitamin D to facilitate calcium absorption. One study found that elderly postmenopausal women consuming more that 10 ounces of coffee daily lost more bone in the spine than women consuming less than that amount.[45]

The anticonvulsants carbamazepine, phenobarbital, and phenytoin increase hepatic metabolism of vitamin D to inactive compounds, thereby inhibiting calcium absorption. Consequences can be reviewed in the calcium monograph.

Mineral oil may reduce absorption of both vitamin D and calcium if used on a regular basis. Short-term use is not expected to have a clinically significant effect.[46]

Rifampin increases hepatic metabolism of 25-hydroxy-vitamin D, thereby reducing plasma levels.[47] This has been seen to contribute to osteomalacia with therapy of more than one year, especially in the face of low vitamin D intake or minimal sun exposure.

Stimulant laxatives used for long periods of time and high doses can reduce absorption of dietary vitamin D, leading to reduction in calcium absorption.[48]

Frequent and extensive application of sunscreens has been shown to reduce vitamin D synthesis in the skin. There is concern that overuse of sunscreen can contribute to vitamin D deficiency and increase the risk of some cancers.[49]

4.10.2 Screening, prevention, and treatment

All patients should be encouraged to ingest vitamin D through diet (preferably) or through a supplement that meets the recommendations of the Osteoporosis Society of Canada (see Appendix 2).

For patients taking anticonvulsants listed, calcium and vitamin D should be monitored in those taking these medications for 6 months or more and supplements recommended as appropriate.

If rifampin is taken with isoniazid, its effects of on vitamin D absorption appear to be negated.[50] Otherwise, serum levels of vitamin D should be monitored in people taking rifampin. Clinical effects are more prevalent if the drug is taken for more than one year.

Patients should be reminded that use of mineral oil or stimulant laxatives should be limited to short-term.

The sunscreen issue is a dilemma. Brief sun exposure is not likely dangerous and helps maintain adequate vitamin D levels. However, for longer exposure than a "dose" of dermal vitamin D, the use of a sunscreen with SPF 15 or greater should be recommended.[46]

5. Summary: Pharmacists and drug-induced nutrient depletion

An assessment of potential for drug-induced nutrient depletion should be conducted for each patient receiving a new medication. In addition, any change in the patient's medical circumstances should prompt a review of drugs that may adversely affect that condition in any way, including by virtue of drug-induced nutrient depletion.

In order to assess the potential for nutrient depletion, it is important to consider all contributing factors. Patients already at risk for depletion of a nutrient will be at higher risk for drugs causing or exacerbating the problem. Certain drugs may prompt immediate nutrient supplementation in some patients (see text). Many of the drugs highlighted in this module should prompt close monitoring of symptoms of depletion as well as lab monitoring of nutrient levels. Of critical importance is education of the patient on the evidence-based potential of depletion with a particular drug as well as signs and symptoms to be aware of. The team-based approach to care will be most effective in preventing and/or identifying and resolving issues associated with drug-induced nutrient depletion.

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Appendix 1. Alphabetical listing of drugs and associated potential nutrient depletion[9]

Drug	Nutrients depleted (potential – see text)
acid-reducing agents (gastric)	calcium, phosphorus, vitamin B_{12}
aminoglycosides	magnesium, potassium
aminosalicylic acid	folic acid, niacin and niacinamide, pyridoxine (vitamin B_6)
amphotericin b	magnesium, potassium
antibiotics	intestinal microflora (B vitamins, vitamin K)
carbamazepine	folic acid, vitamin D (calcium)
cholestyramine	beta-carotene, folic acid, vitamins A, D, E, K
cisplatin	carnitine, magnesium, potassium, vitamin E, zinc
colchicines	beta-carotene, vitamin B_{12}
corticosteroids	calcium, potassium
digoxin	magnesium
estrogens	folic acid, magnesium, pyridoxine (vitamin B_6)
fluoroquinolones	calcium, iron
hydralazine	pyridoxine (vitamin B_6)
isoniazid	pyridoxine (vitamin B_6)
loop diuretics	calcium, magnesium, potassium, sodium, thiamine, zinc
magnesium salts	calcium, phosphorus
metformin	vitamin B_{12}
methotrexate	folic acid
mineral oil	vitamins A, D, E, K, beta carotene, calcium
orlistat	vitamins A, D, E, K
penicillamine	copper, iron, magnesium, pyridoxine (vitamin B_6), zinc
penicillins (sodium-containing only)	potassium
pentamidine	folic acid, magnesium
phenobarbital	folic acid, vitamin D (calcium), vitamin K
phenytoin	folic acid, vitamin D (calcium), vitamin K, thiamine
rifampin	vitamin D, vitamin K
sodium phosphates	magnesium, potassium
statins	coenzyme Q_{10}
stimulant laxatives	calcium, sodium, potassium, vitamin D
sucralfate	phosphate salts
sulfasalazine	folic acid
sunscreens	vitamin D
tetracyclines	calcium, iron
theophylline	potassium, pyridoxine (vitamin B_6)
thiazide diuretics	magnesium, sodium, potassium, zinc
thyroid hormones	calcium
triamterene	folic acid
trimethoprim	folic acid
valproic acid	carnitine

Appendix 2: Major functions, daily requirements, and good food sources of vitamins[51]

Vitamin	RDA or AI*			Major functions	Good food sources
Fat-soluble vitamins					
vitamin A (retinol, provitamin carotenoids) 0.3 µg = 1 IU vit A		µg/day		prevents night blindness, intestinal infections, impaired growth, dryness and thickening of surface of conjunctiva and cornea of the eyes	milk, cheese, liver, carrots, green leafy vegetables, sweet potatoes, mango, apricots
		Males	Females		
	0–6 mos	400*	400*		
	7–12 mos	500*	500*		
	1–3 yrs	300	300		
	4–8 yrs	400	400		
	9–13 yrs	600	600		
	>14 yrs	900	700		
	Pregnancy		770		
	Lactation		1300		
vitamin D 200 IU = 5 µg	Infants, children: 200 IU/day* Adults, as per 2002 Osteoporosis Society of Canada Guidelines: Persons <50 yrs: 400 IU/day Persons ≥50 yrs: 800 IU/day Pregnancy/lactation: 400 IU/day			increases the intestinal absorption of calcium and promotes bone and tooth formation	action of sunlight on skin, dairy products, eggs, salmon
vitamin E (tocopherol)		mg/day		acts as antioxidant to prevent cell walls from breakdown due to oxidation	vegetable oils, wheat germ, green leafy vegetables, egg yolk
		Males	Females		
	0–6 mos	4*	4*		
	7–12 mos	5*	5*		
	1–3 yrs	6	6		
	4–8 yrs	7	7		
	9–13 yrs	11	11		
	>14 yrs	15	15		
	Pregnancy		15		
	Lactation		19		
vitamin K		µg/day		essential for the clotting of blood; promotes good bone health	liver, eggs, spinach, cauliflower; also formed in intestine by bacteria
		Males	Females		
	0–6 mos	2.0*	2.0*		
	7–12 mos	2.5*	2.5*		
	1–3 yrs	30*	30*		
	4–8 yrs	55*	55*		
	9–13 yrs	60*	60*		
	14–18 yrs	75*	75*		
	>18 yrs	120*	90*		
	Pregnancy		90*		
	Lactation		90*		

Vitamin	RDA or AI*			Major functions	Good food sources
Water-soluble vitamins					
vitamin C (ascorbic acid)		mg/day		forms collagen, aids iron absorption, acts as antioxidant, helps with production of adrenaline	citrus fruits, green leafy vegetables, broccoli, peppers, strawberries
		Males	Females		
	0–6 mos	40*	40*		
	7–12 mos	50*	50*		
	1–3 yrs	15	15		
	4–8 yrs	25	25		
	9–13 yrs	45	45		
	14–18 yrs	75	65		
	>18 yrs	90	75		
	Pregnancy		85		
	Lactation		120		
vitamin B_1 (thiamine)		mg/day		essential for nervous system function; helps with energy production from carbohydrates	meat products, whole-grain fortified breads and cereals, legumes
		Males	Females		
	0–6 mos	0.2*	0.2*		
	7–12 mos	0.3*	0.3*		
	1–3 yrs	0.5	0.5		
	4–8 yrs	0.6	0.6		
	9–13 yrs	0.9	0.9		
	14–18 yrs	1.2	1.0		
	>18 yrs	1.2	1.1		
	Pregnancy		1.4		
	Lactation		1.4		
vitamin B_2 (riboflavin)		mg/day		helps with energy production from carbohydrates and fats; helps maintain healthy skin	milk and dairy, meat, fortified grains, green leafy vegetables, beans
		Males	Females		
	0–6 mos	0.3*	0.3*		
	7–12 mos	0.4*	0.4*		
	1–3 yrs	0.5	0.5		
	4–8 yrs	0.6	0.6		
	9–13 yrs	0.9	0.9		
	14–18 yrs	1.3	1.0		
	>18 yrs	1.3	1.1		
	Pregnancy		1.4		
	Lactation		1.6		

Vitamin	RDA or AI*			Major functions	Good food sources
vitamin B_3 (nicotinamide, nicotinic acid, niacin)		mg/day		helps with energy production from carbohydrates; helps build fat and block release of free fatty acids; needed for healthy skin	meats, fish, poultry, whole-grains, beans; formed in the body from tryptophan
		Males	Females		
	0–6 mos	2*	2*		
	7–12 mos	4*	4*		
	1–3 yrs	6	6		
	4–8 yrs	8	8		
	9–13 yrs	12	12		
	>14 yrs	16	14		
	Pregnancy		18		
	Lactation		17		
vitamin B_6 (pyridoxine)		mg/day		helps with protein metabolism, necessary for red blood cell and hemoglobin formation, release of glucose from glycogen, and formation of glucose by liver	protein foods, legumes, green leafy vegetables, bananas, figs
		Males	Females		
	0–6 mos	0.1*	0.1*		
	7–12 mos	0.3*	0.3*		
	1–3 yrs	0.5	0.5		
	4–8 yrs	0.6	0.6		
	9–13 yrs	1.0	1.0		
	14–18 yrs	1.3	1.2		
	19–30 yrs	1.3	1.3		
	31–50 yrs	1.3	1.3		
	>50 yrs	1.7	1.5		
	Pregnancy		1.9		
	Lactation		2.0		
vitamin B_{12} (cyanocobalamin, methylcobalamin)		µg/day		helps with formation of DNA, and red blood cell development as well as maintenance of nerve tissue	animal foods only; meat, fish, poultry, eggs, milk
		Males	Females		
	0–6 mos	0.4*	0.4*		
	7–12 mos	0.5*	0.5*		
	1–3 yrs	0.9	0.9		
	4–8 yrs	1.2	1.2		
	9–13 yrs	1.8	1.8		
	>13 yrs	2.4	2.4		
	Pregnancy		2.6		
	Lactation		2.8		

Vitamin	RDA or AI*			Major functions	Good food sources
folic acid (folate)		µg/day		helps with DNA formation and red blood cell development	liver, green leafy vegetables, legumes, nuts, fortified grains
		Males	Females		
	0–6 mos	65*	65*		
	7–12 mos	80*	80*		
	1–3 yrs	150	150		
	4–8 yrs	200	200		
	9–13 yrs	300	300		
	>13 yrs	400	400		
	Pregnancy		600		
	Lactation		500		
biotin (AI values)*		µg/day		helps with metabolism of carbohydrates, fats and protein	meats, legumes, milk, egg yolk, whole-grains, most vegetables
		Males	Females		
	0–6 mos	5*	5*		
	7–12 mos	6*	6*		
	1–3 yrs	8*	8*		
	4–8 yrs	12*	12*		
	9–13 yrs	20*	20*		
	14–18 yrs	25*	25*		
	>18 yrs	30*	30*		
	Pregnancy		30*		
	Lactation		35*		
pantothenic acid (AI values)*		mg/day		part of coenzyme A used in energy metabolism	meats, milk, eggs, legumes, whole grains, most vegetables
		Males	Females		
	0–6 mos	1.7*	1.7*		
	7–12 mos	1.8*	1.8*		
	1–3 yrs	2*	2*		
	4–8 yrs	3*	3*		
	9–13 yrs	4*	4*		
	>13 yrs	5*	5*		
	Pregnancy		6*		
	Lactation		7*		

RDA= Recommended Dietary Allowance AI = Adequate Intake

Appendix 3: RDA/AI, major functions, and good food sources of minerals[51]

Mineral	RDA or AI*	Major functions	Good food sources
calcium†	Pre-pubertal: 800 mg Adolescents (9–18): 1300 mg Women, men (19–50): 1000 mg Women, men (>50): 1500 mg Pregnant, lactating 1000 mg	bone formation, enzyme activation, nerve transmission, muscle contractions	milk, hard cheeses, yogurt, sardines with bones, broccoli, cabbage, almonds, sunflower seeds, molasses, figs, white beans
iron	mg/day Males / Females 0–6 mos: 0.27* / 0.27* 7–12 mos: 11 / 11 1–3 yrs: 7 / 7 4–8 yrs: 10 / 10 9–13 yrs: 8 / 8 14–18 yrs: 11 / 15 19–30 yrs: 8 / 18 31–50 yrs: 8 / 18 >50 yrs: 8 / 8 Pregnancy: 27 Lactation: 9	requirement for hemoglobin and myoglobin production in the blood (oxygen transport), oxidative processes	liver, oysters, trout, sardines, beef, pork, lamb, egg yolk, iron-enriched cereals, legumes, nuts, seeds, dried figs, prunes, dates, raisins, canned tomatoes, tofu, leafy green vegetables, broccoli, whole grains
magnesium	mg/day Males / Females 0–6 mos: 30* / 30* 7–12 mos: 75* / 75* 1–3 yrs: 80 / 80 4–8 yrs: 130 / 130 9–13 yrs: 240 / 240 14–18 yrs: 410 / 360 19–30 yrs: 400 / 310 >31 yrs: 420 / 320 Pregnancy: 350 Lactation: 310	bone component, protein production, glucose metabolism, smooth muscle contraction	legumes (including tofu), nuts, seeds, avocado, whole grains, wheat germ, baked potato, milk cheese, yogurt, banana, raisins, green peas, leafy green vegetables, broccoli

Mineral	RDA or AI*			Major functions	Good food sources
zinc		mg/day		helps the action of many enzymes involved in energy metabolism, protein production, immune function, sexual maturation, sensations of smell and taste	liver, beef, pork, lamb, poultry, whole grains, wheat germ, legumes, peanuts, seeds, milk, cheese, yogurt, eggs, seafood, sardines, herring, leafy green vegetables
		Males	Females		
	0–6 mos	2*	2*		
	7–12 mos	3	3		
	1–3 yrs	3	3		
	4–8 yrs	5	5		
	9–13 yrs	8	8		
	14–18 yrs	11	9		
	>19 yrs	11	8		
	Pregnancy		12		
	Lactation		12		
phosphorus		mg/day		bone formation, acid-base balance, cell wall structure, B vitamin activation, component of ATP (energy)	meat products, tofu, milk
		Males	Females		
	0–6 mos	100*	100*		
	7–12 mos	275*	275*		
	1–3 yrs	460	460		
	4–8 yrs	500	500		
	9–18 yrs	1250	1250		
	>18 yrs	700	700		
	Pregnancy		700		
	Lactation		700		
selenium		mg/day		antioxidant, works along with enzyme glutathione peroxidase and vitamin E to prevent production of destructive molecules	liver, kidneys, seafood, beef, pork, lamb, whole grains, milk, cheese, yogurt, fruits, vegetables
		Males	Females		
	0–6 mos	15*	15*		
	7–12 mos	20*	20*		
	1–3 yrs	20	20		
	4–8 yrs	30	30		
	9–13 yrs	40	40		
	>13 yrs	55	55		
	Pregnancy		60		
	Lactation		70		

Mineral	RDA or AI*			Major functions	Good food sources
iodine		µg/day		helps in formation of thyroid hormones	iodized salt, seafood, vegetables
		Males	Females		
	0–6 mos	110*	110*		
	7–12 mos	130*	130*		
	1–3 yrs	90	90		
	4–8 yrs	90	90		
	9–13 yrs	120	120		
	>13 yrs	150	150		
	Pregnancy		220		
	Lactation		290		
copper		µg/day		blood cell and connective tissue formation	lean beef and poultry
		Males	Females		
	0–6 mos	200*	200*		
	7–12 mos	220*	220*		
	1–3 yrs	340	340		
	4–8 yrs	440	440		
	9–13 yrs	700	700		
	>13 yrs	900	900		
	Pregnancy		1000		
	Lactation		1300		
manganese		mg/day		involved in formation of bone, as well as in enzymes involved in amino acid, cholesterol, and carbohydrate metabolism	widespread in plant foods (deficiencies are rare)
		Males	Females		
	0–6 mos	.003*	.003*		
	7–12 mos	0.6*	0.6*		
	1–3 yrs	1.2*	1.2*		
	4–8 yrs	1.5*	1.5*		
	9–13 yrs	1.9*	1.6*		
	14–18 yrs	2.2*	1.6*		
	>19 yrs	2.3*	1.8*		
	Pregnancy		2.0*		
	Lactation		2.6*		

Mineral	RDA or AI*			Major functions	Good food sources
fluoride		mg/day		involved in the formation of bones and teeth; inhibits the initiation and progression of dental caries	drinking water (if fluoride containing or fluoridated), tea, seafood; fluoridated toothpaste
		Males	Females		
	0–6 mos	0.01*	0.01*		
	7–12 mos	0.5*	0.5*		
	1–3 yrs	0.7*	0.7*		
	4–8 yrs	1*	1*		
	9–13 yrs	2*	2*		
	14–18 yrs	3*	3*		
	>19 yrs	4*	3*		
	Pregnancy		3*		
	Lactation		3*		
chromium		mg/day		increases the activity of insulin	some cereals, meats, poultry, fish, beer
		Males	Females		
	0–6 mos	0.2*	0.2*		
	7–12 mos	5.5*	5.5*		
	1–3 yrs	11*	11*		
	4–8 yrs	15*	15*		
	9–13 yrs	25*	21*		
	14–18 yrs	35*	24*		
	19–30 yrs	35*	25*		
	31–50 yrs	35*	25*		
	>50 yrs	30*	20*		
	Pregnancy		30*		
	Lactation		45*		
molybdenum		mg/day		cofactor for enzymes involved in catabolism of sulphur amino acids, purines, and pyridines	legumes, cereals, grains and nuts, organ meats
		Males	Females		
	0–6 mos	2*	2*		
	7–12 mos	3*	3*		
	1–3 yrs	17	17		
	4–8 yrs	22	22		
	9–13 yrs	34	34		
	14–18 yrs	43	43		
	>19 yrs	45	45		
	Pregnancy		50		
	Lactation		50		

RDA= Recommended Dietary Allowance AI = Adequate Intake
† Recommended daily amounts according to 2002 Osteoporosis Society of Canada Guidelines

Questions

Questions 1–4 refer to the following case:
Mona K. is a 56-year-old woman who has been in menopause for 4 years. She has moderate-to-severe asthma, hypertension, and dyslipidemia. Her chronic medication regimen includes hydrochlorothiazide 25 mg daily, rosuvastatin 10 mg daily, and budesonide/formoterol 200/6 µg inhaler twice daily and prn. She is in today presenting you with a prescription for prednisone 10 mg once daily for one month. In checking her medication profile you notice that this is her third concurrent refill of this medication.

1. Which of the following recommendations would be appropriate to make to her at this time?
   a. You should add a calcium supplement of 1500 mg daily and vitamin D 800 IU daily to your current medication regimen.
   b. Adding a supplemental magnesium salts in high dose would be advisable at this time.
   c. You should speak with your doctor about the potential need for bone mineral density testing at this time if not already discussed.
   d. Answers a and b are correct.

2. Mona tells you that her doctor has asked her to take a calcium supplement and vitamin D. Which of the following drugs is **least** likely to result in depletion of calcium?
   a. mineral oil
   b. furosemide
   c. magnesium salts
   d. hydrochlorothiazide

3. Mona is inquiring about coenzyme Q_{10} because she has heard it is "good for people who take cholesterol-lowering medication." She asks for your opinion on whether she should take it or not. Which of the following would be your most appropriate recommendation?
   a. While it is true that statins reduce levels of coenzyme Q_{10}, more studies are needed to determine if taking a supplement makes any difference.
   b. Studies have shown that coenzyme Q_{10} levels do decline with statin use and that supplementation is advisable with more potent statins such as rosuvastatin.
   c. Studies have shown that coenzyme Q_{10} levels do decline with statin use and that supplementation is advisable with any statin therapy.
   d. Studies have shown that coenzyme Q_{10} levels do decline with statin use and that supplementation should be weighed against the many risks associated with coenzyme Q_{10} therapy.

4. If Mona does decide to purchase coenzyme Q_{10}, which of the following doses would be most appropriate?
   a. 50 mg daily
   b. 150 mg daily
   c. 250 mg daily
   d. 350 mg daily

Questions 5–8 refer to the following case:
Harry J. is a 66-year-old retired postal worker who has type 2 diabetes (treated for 5 years) and rheumatoid arthritis (treated for 7 years). He takes methotrexate 7.5 mg once weekly, metformin 500 mg 3 times daily, atorvastatin 10 mg daily, and amlodipine 5 mg daily. He has recently had a lab test reveal that he is low in vitamin B_{12}, folic acid, and iron.

5. Harry's doctor calls to ask what dose of folic acid you would recommend for supplementation. Which of the following would be most appropriate?
   a. 1 mg daily
   b. 5 mg daily
   c. 10 mg weekly
   d. answers a and/or b would be appropriate

6. Which of the following would be signs of folic acid depletion in Harry?
   a. tingling and numbness in hands and feet
   b. increased appetite
   c. reduced homocysteine levels
   d. answers a and c are correct

7. Harry's doctor would like to supplement his iron intake. Which of the following iron supplement contains the highest percentage of elemental iron?
   a. ferrous fumarate
   b. ferrous sulfate
   c. ferrous gluconate
   d. they are all approximately equal

8. Harry asks you if his diabetes drug might have caused any of his nutrient issues. Which of the following would be your most appropriate response?
   a. Yes, metformin has been known to reduce iron or vitamin B_{12} levels in about 10% of people taking them for more than a few years.
   b. Yes, metformin has been known to reduce folic acid levels in over one-half of patients who take it for more than a few years.
   c. Yes, metformin has been known to reduce vitamin B_{12} in about 20% of patients who take it for more than a few years.
   d. Yes, metformin has been known to reduce iron in about 30% of patients who have taken it for more than a few years.

Questions 9–15 refer to the following case:
Linda R. is a 34-year-old mother of a 4-year-old child (Mark) with a seizure disorder. Mark is currently taking valproic acid to control his seizures.

9. Linda has read that valproic acid can cause carnitine deficiency and is concerned about her son. Which of the following carnitine-related adverse effects occurs in high incidence in young children using valproic acid?
   a. renal failure
   b. hepatotoxicity
   c. osteomalacia
   d. inflammatory bowel disease

10. You thank Linda for her concern and recommend that her doctor be contacted to consider beginning Mark on a preventive dose of oral L-carnitine. Which of the following doses would you recommend?
   a. 25 mg/kg/day
   b. 50 mg/kg/day
   c. 75 mg/kg/day
   d. 100 mg/kg/day

11. Linda asks you for a refill of her oral contraceptive. She takes no other medication and is in good health. She tells you that she gets "moody," depressed, and lethargic, and wonders if the cause could be pyridoxine depletion caused by her pills. Which of the following is your most appropriate response?
   a. Estrogens do reduce pyridoxine levels, and a dose of pyridoxine 25–50 mg daily should help with symptoms.
   b. Although oral contraceptives may reduce pyridoxine levels, there isn't much evidence to suggest supplementation helps symptoms.
   c. Pyridoxine supplements in doses of 100–200 mg daily have been found useful in relieving symptoms of depression and lethargy associated with estrogen use.
   d. If you feel numbness and tingling in your hands and feet, you should take pyridoxine supplementation of 75–150 mg daily.

12. Linda is a caregiver for her father, who has been told that his magnesium levels are low. Which of the following drugs from his medication list is the most likely cause of this nutrient depletion?
   a. atorvastatin
   b. carbamazepine
   c. digoxin
   d. trimethoprim

13. Linda asks you about the signs of hypomagnesemia. Which of the following is **not** a common symptom?
   a. bradycardia
   b. muscle cramping
   c. weakness
   d. vertigo

14. The doctor has told Linda that she should try and keep her father's potassium up. He has told her that her father's recent visit to the hospital, where he was administered IV corticosteroids, caused his potassium to drop a bit. Which of the following corticosteroids would be least likely to cause this effect?
   a. fludrocortisones
   b. hydrocortisone
   c. cortisone
   d. methylprednisolone

15. Linda wants to be sure her father's calcium and vitamin D levels are not depleted. Which of the following would be most likely to deplete vitamin D levels when used for extended periods?
   a. theophylline
   b. stimulant laxatives
   c. statins
   d. isoniazid