Drug–Nutrient Interactions

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Prescription and non-prescription drugs have improved the health and well-being of humans. Yet, the potential for alterations in drug performance and/or changes in nutritional status exist. A drug interaction is a situation in which a substance affects the kinetics of a drug or produces a new side effect. Bioactive components in some food have the potential to interact with drugs and either reduce or enhance pharmaceutical effects. Dietary supplements, herbals, and botanicals may contribute additional interactions with drugs. Typically, drug–nutrient interactions are considered adverse side effects [1–4].

> The International Dietetics & Nutrition Terminology Reference Manual [5] defines a food-medication interaction as an 'undesirable or harmful interaction(s) between food and over-the-counter medications, prescribed medications, herbals, botanicals and/or dietary supplements that diminishes, enhances, or alters the effect of nutrients and/or medications.'

Identification of potential risk for drug–nutrient interactions is an essential component of the comprehensive nutrition assessment performed during the nutrition care process. The likelihood of interactions may be increased when the patient is malnourished, has an underlying illness, takes botanical and herbal supplements, consumes alcohol daily, has food allergies or food intolerances, follows a restrictive therapeutic diet, has health beliefs that limit food choices, takes more than two medications, does not follow medication instructions, and/or is a growing child or older adult. Individuals with acute and chronic inflammatory conditions are at risk for sub-optimal serum albumin levels. Albumin is the most important drug-binding protein in the body. Hypoalbuminemia diminishes the number of drug-binding receptor sites and may result in reduced drug bioavailability [3].

It is in the patient's best interest to minimize drug–nutrient interactions. Patients who avoid these interactions are more likely to experience the drug's intended effect and less prone to discontinue taking the drug earlier than recommended. Avoiding drug-induced nutrient deficiencies helps to maintain nutritional status, avoid falls, and injuries that may be caused in part by nutrient imbalances [6, 7].

Not all patients have optimal nutritional status when a new drug is recommended. The undernourished individual may have nutrient insufficiencies that evolve into frank deficiencies due to a drug-induced adverse effect. Malnutrition with loss of lean muscle mass is of concern because of alterations in protein-binding, drug distribution and drug elimination. Drug distribution is the movement of an active drug from the bloodstream to the site of effect. It is affected by a number of factors, including lipophilicity and plasma protein binding. Drug elimination includes metabolism and excretion of the drug.

Malnourished individuals experience loss of fat mass, skeletal muscle mass and visceral muscle mass. The altered body composition has the potential to reduce transport proteins and regulatory hormones involved in drug distribution. The loss of visceral muscle mass contributes to the changes in cardiac output, reduced blood flow to the liver and reduced glomerular filtration rate that may alter drug elimination [8–10].

Individuals taking drugs for a long duration who experience insidious weight loss may be taking drug dosages based on a higher body weight. These individuals are at higher risk for drug–nutrient interactions. In obese patients, there is a risk for accumulation of fat-soluble drugs or a prolonged clearance of drugs resulting in increased risk for drug toxicity.

15.1 Effect of Food and Nutrients on Drug Kinetics and Efficacy

Food and dietary supplements may alter drug kinetics and bioavailability. The bioavailability of a drug is the amount of the drug that reaches systemic circulation. Drugs taken orally have a lower bioavailability than drugs administered intravenously.

The presence of food and nutrients in the stomach and small intestine may increase, decrease or have no effect on the bioavailability of the drug. For example, immediate-release bisphosphonates, such as alendronate sodium, taken with food, significantly reduce drug absorption [11]. However, delayed-release bisphosphonates, such as risedronate delayed-release, may be taken before or after a meal without significantly reducing drug absorption [12].

Furanocoumarins found in grapefruit segments, grapefruit juice, Seville oranges, tangelos, minneolas, and other exotic oranges inhibit the actions of cytochrome P450 enzymes required for oxidative metabolism of numerous drugs. This interaction is of greatest concern for oral drugs with low bioavailability. Moreover, the effects of grapefruit segments and grapefruit juice on the actions of cytochrome P450 enzymes can last up to 72 hours [3, 4].

The presence of food and nutrients in the gut may enhance the drug bioavailability. For example, the absorption of cefuroxime axetil (antibiotic) is increased when taken with a meal versus a fasting state [13]. The bioavailability of iron sulfate supplements is enhanced if taken with food or with ascorbic acid. However, certain food components and nutrients may inhibit iron absorption, including high phytate foods, bran, fiber supplements, coffee, tea, dairy products, and calcium supplements [14, 15].

Drug bioavailability may be altered when achlorhydria or hypochlorhydria persists either due to the action of another drug or because of a medical condition. Drugs used to treat chronic acid suppression raise the pH of the stomach. The higher pH prevents drugs such as ketoconazole (antifungal) from reaching its optimal effect [3, 4]. Table 15.1 summarizes common effects of food and nutrients on drug kinetics.

Table 15.1 Common effect of food and nutrients on drug kinetics

Drug	Food, macronutrient or micronutrient	Potential food–drug interaction
Antibiotics	Milk	Calcium and magnesium in milk may complex with drug and reduce bioavailability [16–18]
Anticonvulsants	Grapefruit juice, grapefruit segments, Seville oranges, tangelos, minneolas, and other exotic oranges	Reduce bioavailability by inhibiting the actions of the cytochrome P450 3A enzymes [19]
Antihypertensives	Licorice	Licorice may cause hypermineralocorticoidism with sodium retention, increased potassium loss, edema, increased blood pressure and depression of the renin-angiotensin-aldosterone system [20]
Calcium channel drugs with Calcium Channe l drugs HMG-CoA Reductase Inhibitors	Grapefruit juice, grapefruit segments, Seville oranges, tangelos, minneolas, and other exotic oranges	Reduce bioavailability by inhibiting the actions of the cytochrome P450 3A enzymes required for oxidative metabolism of numerous drugs [3, 4, 19]
Celiprolol (beta-blocker)	Orange juice	Hesperidin, present in orange juice, is responsible for the decreased absorption [21]
Monoamine oxidase inhibitors	Tyramine-containing foods	Consuming foods containing tyramine with MAOI may trigger a hypertensive crisis [22]
Psychotropics	Grapefruit juice	Components in grapefruit juice interfere with the intestinal efflux transporter P-glycoprotein (P-gp) [23, 24]
Warfarin	Foods rich in vitamin K	Inconsistent intakes of vitamin K rich foods may alter the effectiveness and safety of warfarin [25, 26]
	Cranberry juice	Consumption of cranberry juice is reported to alter the effectiveness and safety of warfarin in some individuals [27, 28]

15.2 Effect of Drugs on Food and Nutrient Kinetics and Nutrition Status

Drugs have the potential to alter food and nutrient intake and kinetics. Nutrients are essential for metabolic processes, and micronutrients reserves, or pools, are quickly depleted when the metabolic rate is increased, absorption and utilization of key nutrients are reduced, or excretion of nutrients is increased.

Drugs have the potential to impact nutrition status in many ways. Many prescription and non-prescription drugs reduce appetite, which reduces total nutrient intake. Other drugs increase the appetite for all food or specific categories of foods, e.g., refined carbohydrates, resulting in excessive energy and refined sugar intake. Moreover, drugs can reduce the absorption of key nutrients in the gastrointestinal tract in a variety of ways, including altering the stomach pH, binding the nutrient into an unusable form, and damaging the absorptive surfaces.

Drugs may increase the metabolism of nutrients, thereby increasing requirements and depleting nutrient reserves. Moreover, drugs may block the conversion of a pre-vitamin to its active form. Key nutrients may be lost in urine and feces. Drugs may increase or decrease urinary excretion. An increase in urinary excretion is typically due to a reduction in reabsorption of the nutrient. Drugs that decrease normal nutrient excretion of sodium may result in water retention.

Drugs that cause damage to the absorptive surfaces have the greatest potential to affect nutrient absorption. Common offenders include chemotherapeutic agents, nonsteroidal anti-inflammatory drugs, and prolonged antibiotic therapy. Table 15.2 summarizes potential drug-induced nutrient deficiencies.

15.3 Role of the Nutrition Professional

Malnutrition and nutrient deficiencies are often viewed as problems unique to developing countries and regions of the world affected by environmental disasters, famine, or political unrest. However, malnutrition and nutrient deficiencies are seen globally. Malnutrition diagnoses may be overlooked because the medical team is not mindful of the potential for nutrient losses to occur. It is essential to recognize that some drug-induced nutrient insufficiencies and deficiencies are insidious and others develop quickly. Drug-induced nutrient deficiencies are compounded by malnutrition. The early signs and symptoms of nutrient insufficiencies and deficiencies are often nonspecific and may be overlooked or misdiagnosed. Laboratory assessments used concurrently with

Table 15.2 Common effects of drugs on food and nutrient kinetics

Drug category	Macronutrient or micronutrient loss	Potential consequences of food–drug interaction
Antacids, magnesium and aluminum, calcium carbonate, proton pump inhibitors (PPI)	Calcium, magnesium, phosphorus, folic acid, copper, iron, vitamin B12	Increased stomach pH and reduced absorption of key nutrients that are best absorbed in the duodenum with a low pH including folic acid [29], calcium, phosphorus, copper, and iron [30, 31]
		It is unclear how PPI's promote hypomagnesemia [30–32]
		Aluminum can bind the phosphate in small intestine, thus lowering serum levels. The body responds by releasing calcium and phosphorus stores from the bones. Calcium levels are tightly controlled in the blood. Excess calcium is excreted in the urine [30]
		Increased pH impairs the body's ability to cleave vitamin B12 from its protein carrier in order to be transported via intrinsic factor (IF). IF is synthesized by the parietal cells in the stomach in the presence of a low pH. An increased pH reduces the synthesis of IF, which will result in reduced absorption of vitamin B12 [33]
Antiarrhythmic: digoxin	Magnesium	Digoxin promotes increased renal excretion of magnesium [34]
Antibiotics, sulfonamide combination drugs	Folic acid	May interfere with folic acid metabolism if taken for a prolonged period of time [35]
Antibiotics, fluoroquinolones	Magnesium, iron, zinc, calcium	Drug binds to iron, magnesium, zinc, and calcium creating insoluble complexes [36, 37]
Antibiotics, tetracyclines	Magnesium, iron, zinc, calcium, vitamin K, B complex vitamins	Drugs binds to iron, magnesium, zinc, and calcium creating insoluble complexes. May reduce bacterial synthesis of vitamin K2, menaquinone, in the colon. Long-term use may result in depletion of B vitamin stores [38]
Anticonvulsants	Vitamin B6, vitamin B12, folate	May interfere with vitamin B6, vitamin B12, and folate absorption, resulting in lower serum levels [39, 40]
Anticonvulsants	Biotin	May accelerate catabolism of biotin resulting in lower serum levels [41]
Anticonvulsants	Vitamin D	Lower serum levels reported possibly related to low bone density and osteomalacia [42]
Anticonvulsants	Calcium	Reduced absorption possibly related to vitamin D deficiency [43]
Anticonvulsants	Vitamin K	Drugs may decrease half- life of vitamin K and impair its key functions [44, 45].
Antihyperglycemic metformin	Vitamin B12	Metformin appears to inhibit the absorption of vitamin B12 [46]
Antihypertensive: ACEI angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker	Zinc	ACEI and ARB therapy has been shown to increase urinary excretion of zinc [47]
Antihypertensive: ACEI angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker	Potassium	ACEI and ARBs are associated with increased serum potassium, which may or may not be offset by the reduction of potassium due to loop diuretics [48, 49]
Antihypertensive: hydralazine	Vitamin B6, copper	Hydralazine may interfere with vitamin B6 metabolism. It may promote increased excretion of copper [50, 51]
Antihypertensive: RAAS renin-angiotensin-aldosterone system	Potassium	RAAS have the potential to cause hyperkalemia by interfering with the production and secretion of aldosterone [52–56]
Antimanic: lithium	Sodium	Lithium may increase sodium excretion [57]

Table 15.2 (continued)

Drug category	Macronutrient or micronutrient loss	Potential consequences of food–drug interaction
Antineoplastic: methotrexate	Folic acid	Methotrexate is a folic acid antagonist that interferes with nutrient utilization [58, 59]
Antiplatelet agents	Iron, folic acid, sodium, potassium, vitamin B12	Long-term use associated with reduced levels of iron, folic acid, sodium, potassium, vitamin B12 [60, 61]
Antipsychotics, phenothiazine class, tricyclic antidepressants	Riboflavin	Drug increases the excretion of riboflavin that may lead to deficiency in individuals with insufficient riboflavin intakes [62]
Antitubular: isoniazid	Vitamin B6, niacin (B3), vitamin D, calcium, phosphate	Drug may deplete vitamin B6 and niacin stores resulting in peripheral neuropathy and pellagra [63, 64]
		May impair vitamin D metabolism and consequently reducing calcium and phosphate absorption [65]
Beta-adrenergic blockers (beta-blockers)	Potassium	Beta-blockers have the potential to cause hyperkalemia by causing redistribution of potassium from the intracellular space into the serum [66, 67]
Beta-2 agonists	Magnesium, potassium	Reduced serum levels of magnesium and potassium reported. The degree of deficiency is exacerbated when beta-2 agonist is taken with theophylline [68, 69]
Bile acid sequestrants	Vitamins A, D, E, K, beta-carotene, iron	Bile acid sequestrants bind fat soluble vitamins, beta-carotene, and iron [70]
Bile acid sequestrants	Magnesium, iron, calcium, zinc and folic acid	Alterations in calcium, magnesium, and zinc metabolism may be explained by inadequate vitamin D absorption in the duodenum followed by an increased secretion of parathyroid hormone [71]
Bronchodilator: theophylline	Vitamin B6, potassium, magnesium	Reduced levels of pyridoxal phosphate may be related to altered tryptophan metabolism or impaired vitamin B6 utilization. Reduced levels of potassium and magnesium have been reported, possibly related to increase urinary excretion [72–75]
Colchicine (antigout)	Vitamin B12	In animals, colchicine may reduce vitamin B12 absorption and efficiency of ileal receptor sites leading to a vitamin B12 insufficiency or deficiency [76, 77]
Diuretics: loop	Sodium	Loop diuretics reduce sodium reabsorption in the proximal tubule. Patients who are prescribed a sodium-restricted diet as part of medical management of hypertension are at greater risk of hyponatremia [57]
Diuretics: loop	Potassium	Loop diuretics reduce potassium reabsorption at the site of action and enhance potassium secretion in the distal tubules of the nephron. In addition, aldosterone can also contribute to hypokalemia after administration of loop diuretics [78]
Diuretics: loop	Magnesium	Loop diuretics reduce magnesium reabsorption in the loop of Henle and proximal tubule. It is also dependent on sodium and chloride concentrations. Magnesium depletion promotes the efflux of potassium from cells and subsequent urinary excretion [79–81]
Diuretics: loop	Thiamine	Long-term use is associated with reduced levels of thiamine. Loop diuretics promote thiamine losses up to twice baseline loss. Increased loss is associated with an increase in urine flow rate, but it is not related to sodium excretion. Up to 1/3 of CHF patients were found to be thiamine deficient [82–88]
Diuretics: loop	Zinc	Long-term use of loop diuretics reduce zinc reabsorption in the proximal tubule [89]
Diuretics: loop	Calcium	Loop diuretics reduce calcium reabsorption in the proximal tubule. It is also dependent on sodium and chloride concentrations [90]
Diuretics: thiazide	Calcium	Thiazide diuretics reduce calcium reabsorption in the proximal tubule. It is also dependent on sodium and chloride concentrations [90]

(continued)

Table 15.2 (continued)

Drug category	Macronutrient or micronutrient loss	Potential consequences of food–drug interaction
Diuretics: thiazide	Sodium	Thiazide diuretics reduce sodium reabsorption in the proximal tubule. Patients who are prescribed a sodium-restricted diet as part of medical management of hypertension are at greater risk of hyponatremia [57]
Diuretics: thiazide	Potassium	Thiazide diuretics reduce potassium reabsorption at the site of action and enhance potassium secretion in the distal tubules of the nephron. In addition, aldosterone can also contribute to hypokalemia after administration of loop diuretics [91]
Diuretics: thiazide	Magnesium	Thiazide diuretics reduce magnesium reabsorption in the loop of Henle and proximal tubule. It is also dependent on sodium and chloride concentrations. Magnesium depletion promotes the efflux of potassium from cells and subsequent urinary excretion [79–81]
Diuretics: thiazide	Zinc	Long-term use of thiazide diuretics reduce zinc reabsorption in the proximal tubule [92]
Glucocorticoids	Zinc	Glucocorticoids may promote development of zinc deficiency in some patients [89, 90]
Glucocorticoids	Calcium, Chromium	Glucocorticoids increase urinary losses of chromium and calcium [93, 94]
Immunosuppressant: cyclosporine	Magnesium	Cyclosporine promotes renal magnesium wasting [95]
Immunosuppressant: Hydroxychloroquine	Vitamin D	Hydroxychloroquine may inhibit the conversion of 25-hydroxyvitamin D to the active form, i.e., 1,25 dihydroxyvitamin D [96]
Laxatives, cathartics	Calcium, potassium	Laxatives reduce transit time in the gut leading to diarrhea and increased fecal loss of calcium and potassium [97]
Mineral oil laxatives	Vitamins A, D, E, K	Mineral oil-based laxatives may reduce the absorption of fat soluble vitamins [98]
Peripheral vasodilator	Vitamin B6	Peripheral vasodilators interfere with vitamin B6 metabolism and may result in lower levels [50, 99]

nutrition-focused physical exams are essential tools to detect drug-induced nutrient insufficiencies and deficiencies.

The nutrition professional's approach to detect drug-induced nutrient insufficiencies and deficiencies is determined by the patient's health history. For example, patients who are starting on a new drug are looked at prospectively. The nutrition professional uses clinical judgment to predict the potential for drug-induced nutrient insufficiencies and deficiencies by identifying specific strategies and interventions to prevent or compensate for nutrient losses. Moreover, foods or food intake patterns associated with reduced drug absorption are identified and discussed as part of patient education. The nutrition professional will monitor the readiness of the patient to incorporate specific strategies and interventions as well as the health outcomes. Adjustments in the interventions are often required.

Patients who have been on specific drugs for an extended period of time are assessed retrospectively. The nutrition professional uses clinical judgment to detect signs and symptoms of drug-induced nutrient insufficiencies and deficiencies using historical data. Trends in laboratory results may indicate suspected nutrient insufficiencies that are confirmed with nutrition-focused physical exam. Specific interventions are recommended by the nutrition professional to compensate for nutrient losses. Monitoring and evaluation of changes in nutrition status are essential to determine the efficacy of interventions.

The nutrition professional does not work in a vacuum. As a member of an integrative healthcare team, the nutrition professional provides valuable insight and findings to improve the health and well-being of patients.

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