

# Drug Therapy and Role of Nutrition

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The nutritional status of patients and the constituents of their diet can significantly impact a drug's pharmacokinetic and pharmacodynamic properties.<sup>1</sup> These can affect the absorption, distribution, metabolism, transport, and excretion of drugs. Body weight and/or surface area are also important determinants of proper dosages, and abnormal body composition may impact proper drug dosing. Various nutritional components can impact gastrointestinal (GI) motility, blood flow rates, gastric secretions, and enzymatic activity, ultimately affecting drug metabolism and disposition. These interactions, however, are highly variable, complex, and often difficult to predict. Susceptibility to drug-induced nutrient deficiency appears to be greater during periods of increased requirements (ie, during growth, pregnancy, and lactation). When developing a therapeutic plan for the pediatric patient, it is important that practitioners consider the interactions that occur between nutritional status, age, disease state, and drug action. This chapter discusses the developmental changes that occur in the pharmacokinetics and pharmacodynamics of drugs and presents a discussion on the impact of nutrition on these factors. By definition, pharmacokinetics is the action of drugs in the body over a period of time, including the processes of absorption, distribution in tissues, metabolism, and elimination. This contrasts with pharmacodynamics, which is the study of the biochemical and physiologic effects of drugs and the mechanisms of their actions, including the correlation of actions and effects of drugs with their chemical structure, as well as the effects on the actions of another drug or nutrient. Figure 1 provides an example of the age-dependent variation in pharmacokinetic and pharmacodynamic properties. It should be remembered, however, that in the pediatric patient, in addition to true pharmacokinetic and pharmacodynamic differences, some alterations in drug response may be due to perception as medications are often not adequately studied in children of different ages and different disease states. Thus, there may be difficulties in assessing small but significant differences in medication response because limitations associated with conventional outcome measures.

## DEVELOPMENTAL CHANGES IN BODY COMPOSITION

Unlike the adult, the pediatric patient is undergoing tremendous growth and development. Children should not be thought of as “little adults”

because there are a number of developmental aspects that must be considered when approaching pediatric therapeutics. In fact, during the first decade of life, growth is erratic and does not follow a linear path, thus making simplified dosing approaches inappropriate.<sup>3</sup> Drug–receptor interactions, ontogenetic changes in receptor number, receptor affinity, receptor–effector coupling, and receptor modulation and regulation change as the child grows.<sup>4</sup> Moreover, during infancy and childhood, the proportions of body weight contributed by fat, protein, intracellular water, and extracellular water change dramatically. In the full-term neonate, total body water comprises approximately 70 to 80% of body weight.<sup>5</sup> By age 5 months, this decreases to 60%. From infancy to young adulthood, extracellular water

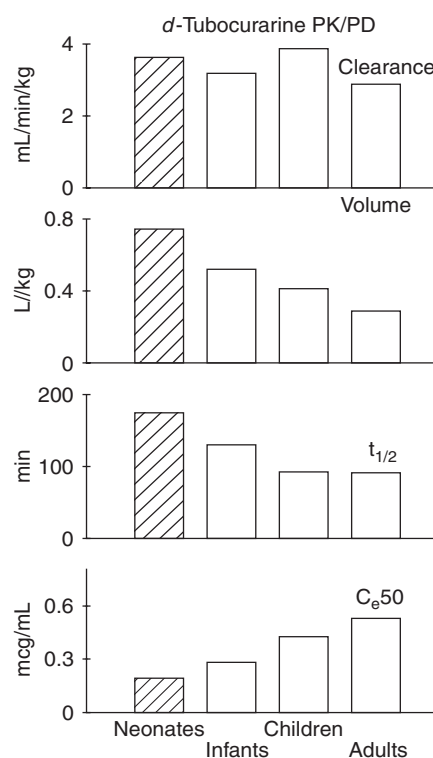
decreases, although the percentage of total body water does not change significantly. In addition, neonates have reduced muscle mass, lower concentrations of albumin, and less intracellular fluid than adults.<sup>6</sup> The change in body water content may significantly affect the volume of distribution of drugs, especially those that are highly hydrophilic. Changes in serum protein (eg, albumin) may alter the free concentration of certain drugs and thus change the patient's pharmacodynamic response. During the second year of life, fat mass is reduced with a corresponding increase in protein mass. For additional information, refer to chapter which reviews the differences in body composition in premature infants, neonates, and adults.

As the child grows, there is a corresponding change in liver and kidney size, with each organ reaching maximum relative size for weight in the 1- to 2-year-old child, when the capacity for drug metabolism and elimination is high.<sup>4</sup> For example, in the term infant, the glomerular filtration rate (GFR) is approximately 2 to 4 mL/min/1.73 m<sup>2</sup>, whereas a premature infant may be as low as 0.6 to 0.8 mL/min/1.73 m<sup>2</sup> and adult values are achieved within the first 8 to 12 months of life.<sup>3</sup> In the infant and young child, body surface area is greatest relative to body mass in comparison with the older child or young adult. As a percentage of adult norms, intestinal length in infants and children exceeds other anthropometric measurements.<sup>3</sup> Furthermore, the absorptive surface of small intestine is proportionately greater, whereas GI transit time is shorter.

During adolescence, there is an approximately 25% increase in height, whereas weight nearly doubles.<sup>4</sup> In prepubertal males and females, lean body mass, skeletal mass, and body fat per unit body weight are similar, but, by maturity, women have twice as much fat relative to total body weight in comparison with adult men.

## FACTORS THAT IMPACT DRUG KINETICS

The aforementioned differences in body composition in the pediatric population are an important consideration when determining the pharmacokinetics of a given medication (Table 1). Nutrients and drugs delivered via the GI tract need to go through an absorption phase prior to reaching the systemic circulation and the sites of action.



**Figure 1** Age-dependent variability in the pharmacodynamic and pharmacokinetic properties of *d*-tubocurarine. In this example, neonates require significantly lower plasma concentrations of *d*-tubocurarine to achieve 50% paralysis in comparison to older children and adults, suggesting that neonates have increased receptor sensitivity. The larger volume of distribution in the neonate may also account for the prolonged half-life, although plasma clearance is comparable in all four age groups. (Adapted from reference 2.)

**Table 1 Factors Associated with Differences in Pharmacokinetic/Pharmacodynamic Parameters in Neonates versus Adults**

Altered receptor sensitivity
Enhanced intramuscular absorption
Greater blood–brain barrier permeability
Hepatic enzyme immaturity /limited enzyme capacity
Higher gastric pH
Immature renal function
Increased percutaneous absorption
Larger liver/body weight ratio
Limited protein binding capacity
Reduced fat mass
Slower GI absorption/increased gastric emptying time

Absorption from the GI lumen into the hepatic portal vein and subsequently to the systemic circulation is a series of complex processes including the dissolution of the solid dosage form, passing of the chyme along the GI tract (ie, gastric emptying and intestinal transit), passive diffusion, active transport, and presystemic metabolism of the compounds. Each of these processes alone may affect the pharmacokinetics of the drug.

### GASTRIC EMPTYING AND INTESTINAL TRANSIT

The oral route continues to be the most widely used route of administration in the pediatric patient. As a result, intraluminal pH in different areas of the GI tract can impact medication stability and extent of drug absorption. Neonates typically have a higher gastric pH (greater than 4) and thus acid labile drugs such as penicillin G are more bioavailable and lower doses can be used, whereas weakly acidic drugs such as phenobarbital require much larger oral doses to reach therapeutic levels.<sup>3</sup> With the exception of a few acidic drugs (eg, aspirin), maximal absorption of most drugs and nutrients takes place in the small bowel. Therefore, gastric emptying and intestinal transit time have a significant impact on the rate and magnitude of the oral absorption of the drugs and certain nutrients.

Gastric emptying time changes in early postnatal life and is likely one of the many explanations for erratic drug absorption rate and oral bioavailability in infants and young children.<sup>7</sup> During infancy, the rate of drug absorption is slower than in older children. As the intestinal tract matures, antral contractions improve and with it a marked increase in gastric emptying. Similarly, intestinal motor activity increases in amplitude and frequency as well as duration of contractions.<sup>3</sup> In addition, gastric acid secretion is low in infants and does not reach the normal adult gastric pH until 3 to 7 years of age.<sup>7</sup>

The lack of developed physiologic regulation of GI motility and gastric acidity during infancy and early childhood suggests that the oral route may not be a reliable route for optimal drug delivery. For instance, delayed absorption and/or

decreased bioavailability have been observed for acetaminophen, phenytoin, and phenobarbital in young children.<sup>8</sup>

As the child continues to grow, GI motility increases by both neuronal and hormonal input.<sup>9</sup> Vagal stimulation increases upper gastric contraction and decreases pyloric sphincter and duodenal contractions. As a result, gastric emptying is promoted and the time it takes for the drug or nutrient to reach the small intestine is shortened. For drugs that are absorbed in the small intestine, this action can result in shortening the time of reaching peak plasma concentration and may promote faster onset of drug action. In addition, because of the decrease in intestinal motility, more complete absorption of the drug may be achieved. Anticholinergic drugs (eg, sedative antihistamines, phenothiazines, tricyclic antidepressants) can reverse these trends by counteracting the effect of the vagus nerve.

### PRESYSTEMIC CLEARANCE

Presystemic clearance, also known as first-pass effect, refers to the removal of orally ingested compounds prior to reaching the systemic circulation. Presystemic effect occurs primarily in the intestine and the liver, whereas the stomach has only a minor role.<sup>10</sup> Type III alcohol dehydrogenase, for example, is present in the gastric mucosa and is responsible for the activation of some biogenic amines and steroids.

Many drug-metabolizing enzymes and active transport proteins are present in the intestinal epithelial tissues. For example, cytochrome P450 (CYP) 3A4 isoenzyme is present in the small bowel and plays a role in the regulation of oral bioavailability of a large number of medications. Induction or inhibition of the enzyme in the gut by nutrients can affect the oral bioavailability of drugs. Certain nutrients are known to affect the enzymatic activity of intestinal CYP3A4 and change the pharmacokinetics of the object drugs. Grapefruit juice is a classic example of an intestinal CYP3A4 inhibitor.<sup>10</sup> Its action is discussed in further detail below. Water-soluble vitamin E (D-alpha-tocopheryl polyethylene glycol succinate) has also been found to increase oral absorption of cyclosporine.<sup>11</sup> The primary mechanism appears to involve inhibition of an intestinal efflux protein, P-glycoprotein (P-gp) instead of intestinal CYP enzymes.<sup>12</sup>

### HEPATIC METABOLISM

The metabolism of a drug involves different steps once it has been absorbed from the GI tract. As drugs are metabolized, they first undergo biotransformation (ie, phase I metabolism), which results in the formation of a more polar compound by oxidation, reduction, hydroxylation, etc. This results in either an activation of the drug or a deactivation. The second phase (ie, phase II reaction) is a synthetic process, involving conju-

gation of the polar compound with endogenous molecules such as glucuronic acid, sulfate, glutathione, glycine, and acetate, resulting in a more hydrophilic compound that is more suitable for excretion into bile or urine.<sup>13</sup> It is important to point out that some drugs do not have to go through phase I metabolism prior to undergoing phase II metabolism. Lorazepam, for example, undergoes phase II metabolism (glucuronidation) by UDP-glucuronosyltransferase (UGT) 2B7 without any phase I reaction involved. The resultant conjugated metabolite is then excreted renally. An enzyme system responsible for the metabolism of most nutrients and drugs is the CYP enzyme superfamily, principally located in the endoplasmic reticulum of the hepatocytes and enterocytes, which is somewhat unique in its ability to use a wide range of substrates.

The maturation of phase I and phase II enzymes varies among individuals. Limited studies suggest that fetal and neonatal CYP, the most important phase I enzyme in metabolizing drugs and biogenic amines and steroids, has about 50 to 70% of the adults' activity and continues to mature throughout childhood. Although some children may have fully matured CYP enzyme activities as early as 6 months of age, it may take up to 12 months for others.<sup>7</sup> For example, the serum half-life of theophylline, a bronchodilator primarily metabolized by CYP1A2 and CYP3A4, is significantly longer in neonates and younger infants than in adults. Similarly, N-demethylation of diazepam, a CYP2C19-mediated pathway, is also significantly slower in infants. There is no well-documented dietary factor known to promote the maturation of these enzymes during the prenatal period and infancy.

### RECTAL ADMINISTRATION

Rectal route of drug administration is an alternative way of drug delivery when the enteral route is not preferable. Unlike the small bowel venous mesentery, the rectal capillary blood supply collects blood directly into the inferior vena cava instead of the hepatic portal vein. Although certain phase II enzymes are present in the colon (eg, UGT1A9), there is no strong evidence to suggest the presence of drug-metabolizing enzyme in the rectum.<sup>14</sup> Hence, presystemic metabolism of the administered drug is prevented. Therefore, compared with oral administration, the relative bioavailability of the drug is usually higher with rectal administration.<sup>15</sup> Drugs that are more commonly delivered rectally in children include anticonvulsants (eg, diazepam), antiemetics (eg, trimethylbenzamide), and sedative agents (eg, chloral hydrate).

### DRUG AND NUTRIENT TRANSPORT SYSTEM

Intestinal transport molecules facilitate the absorption of drugs or nutrients.<sup>16</sup> In addition, some transporters efflux molecules already

absorbed in the cytoplasm of the enterocyte back into the intestinal lumen, thus decreasing the bioavailability of certain compounds. This is believed to be an intrinsic protective mechanism by the host to minimize xenobiotic exposure. P-gp is a representative of this type of efflux system.<sup>17</sup> P-gp belongs to the family of adenosine triphosphate-binding cassette transporters and is an efflux widely distributed in normal tissues, including the intestinal epithelium, renal tubule, liver, and blood–brain barrier. Although no formal studies have been published, nutrients may interact with drugs by either inhibiting or inducing P-gp.

CYP3A4 and P-gp are the two most important limiting factors in regulating the oral bioavailability of drugs.<sup>18</sup> For instance, cyclosporine is a known substrate for both CYP3A4 and P-gp. After oral administration, absorption of cyclosporine across the epithelium in the small intestine is limited by P-gp efflux and prehepatic CYP3A4 metabolism. The P-gp-mediated efflux of cyclosporine from the intestinal cell back into the lumen enables the CYP3A4 enzymes another opportunity to metabolize the drug when it again enters the enterocyte. These mechanisms explain why the oral bioavailability remains poor despite improvement of its formulation to microemulsion.<sup>19</sup> When cyclosporine is coadministered with a CYP3A4 and P-gp inhibitor, such as ketoconazole, erythromycin, or diltiazem, significantly higher maximum blood cyclosporine concentration is observed, indicating an increase in absolute oral bioavailability. Oral bioavailability can be increased by over 40% with concomitant administration of water-soluble vitamin E.<sup>11</sup> The mechanism is mediated through intestinal P-gp inhibition by the formulation. It appears that polyethylene glycol, the surfactant incorporated in the liquid formation, instead of vitamin E is the inhibitor of P-gp.<sup>12,20</sup>

## BINDING INTERACTIONS BETWEEN FEEDINGS AND DRUGS REVISITED

Feeding and food intake are common causes of drug–nutrient interactions. Enteral feeding is the preferred method of providing nutrition support and also allows easy access for administering drugs to patients who are unable to swallow. However, enteral feeding formulas have been implicated in a number of drug–nutrient interactions.<sup>21</sup> Moreover, in children with chronic medical conditions receiving tube feedings, nutrient deficiencies are also a concern because multiple medications and complicated feeding regimens can result in a decrease intake due to feedings being held or due to drug interactions.<sup>22</sup> For example, the oral absorption of warfarin, tetracycline, fluoroquinolone antibiotics, and phenytoin is decreased with concomitant enteral feeding.<sup>23,24</sup> Possible explanations include a decrease in the anticoagulant effect of warfarin caused by increased vitamin K absorption from the enteral formulas or binding of warfarin by a protein component of the enteral formula.<sup>23</sup> It has also been reported that the acidic nature of

most enteral formulas alters the solubility of phenytoin. Phenytoin, a weak acid, is not readily absorbed in acidic conditions and absorption is optimal when it is given in the ionized state. Furthermore, when phenytoin is given with nasogastric feeds, it may become bound to the tubing when it is nonionized in a low pH environment.<sup>25</sup> Drug–nutrient interaction through chelation of divalent and trivalent cations has also been proposed (eg, enteral feeding formulas or dairy products interact with fluoroquinolones).<sup>19</sup> A case of scurvy was reported in a child who received long-term enteral tube feedings using a commercial product. Scurvy occurred owing to the degradation of the ascorbic acid in the formula due to prolonged storage after mixing and from the addition of an iron supplement that further catalyzed the reaction.<sup>26</sup>

Unlike medications given via the oral route, whenever a medication is delivered via feeding tube, tube placement and device characteristics must also be considered. Medications may adhere to the sides of the feeding tube, and thus not be delivered to the patient, or may obstruct the tube in the case of an oral solid not properly pulverized and diluted prior to administration. In some instances, medications are best absorbed in the “fasted” state, requiring that feedings be held so as to optimize absorption. Intra-gastric administration of a medication may delay gastric emptying rates. Medication administration to patients with jejunostomy, nasojejunal, or nasoduodenal-feeding tubes present an additional challenge as these devices bypass the stomach where medications are dissolved and diluted with gastric contents. Due to the narrow bore of the devices and direct administration of medication into the small intestine, liquid medications must be used. Several factors must be considered, however, including the osmolality of the drug, its viscosity, and particle size. Medications that are hypertonic and not diluted prior to administration into the small bowel can result in dumping. The osmolality of stomach secretions is approximately 300 mOsm/kg and many liquid medications exceed this value significantly, resulting in an osmotic induced diarrhea if given in its undiluted state. Whenever a hypertonic medication is given undiluted, gastric emptying rates are altered and there is a flux of water and electrolytes into the small bowel and the absorptive capacity of the small bowel is overwhelmed. Proper dilution of the medication can prevent this flux and improved medication as well as nutrient absorption. Moreover, if the feeding tube does terminate in the jejunum, pH is an important consideration. Enteric-coated products such as lansoprazole and omeprazole need to be dissolved in an alkaline vehicle prior to administration into the jejunum.

## EFFECTS OF MALNUTRITION ON DRUG KINETICS

It has become increasingly recognized that nutritional status is capable of modifying the pharmacologic effect of a medication. Both malnutrition

and obesity can substantially alter drug pharmacokinetics and pharmacologic responses by causing functional and structural alterations in organs that directly affect drug disposition.<sup>27</sup> These changes can affect the absorption, distribution, metabolism, and elimination of a medication that can ultimately affect the therapeutic or toxic response of the drug. Moreover, interindividual and intraindividual variations in the pharmacokinetic responses to a medication can further complicate interpreting the actual impact of altered nutritional status on drug disposition. The variation can be 3- to over 20-fold, depending on genetic (eg, genetic polymorphism) and environmental factors, patient variables, and underlying disease.<sup>27</sup> Pediatric patients, of course, have a higher incidence of undernutrition.

The pathologic changes seen in malnutrition can impact the pharmacokinetics of drugs in all phases of disposition within the body, suggesting that the degree of malnutrition can determine the body’s response to a particular drug. Physiologic changes of protein-energy malnutrition (PEM) may result in alterations in the absorptive capacity of the GI tract, body fluid status, cardiac output, GFR, and plasma protein concentrations, as well as hormonal and metabolic changes. Therapeutic drug levels may be altered as a result of malnutrition-associated tissue receptor alterations.<sup>28</sup> It is conceivable that the risk of toxicities owing to a drug or its metabolites is greater in malnourished patients, with a subsequent risk of morbidity or mortality. This suggests that close drug therapy monitoring and modification of dosage in malnourished patients are imperative. Drugs with narrow therapeutic indices or narrow dose–response curves (ie, phenytoin, theophylline) are particularly susceptible as even small changes in absorption can become significant.

Relatively little is known about the handling of drugs in malnourished children despite the fact that the combination of malnutrition and accompanying disease (typically infection) in need of treatment is a common pediatric problem in many parts of the world. It is possible that the high morbidity of mortality so characteristic of malnutrition may be enhanced by adverse drug reactions.<sup>29</sup>

## ABSORPTION

Little research has been done on the effect of malnutrition on drug absorption. O’Doherty and colleagues observed that phenytoin absorption was slow and erratic in PEM, although the peak concentration and time to reach peak concentration did not differ significantly from controls.<sup>30</sup> Mehta and colleagues reported similar findings with acetaminophen disposition in children suffering from PEM.<sup>31</sup> Like O’Doherty and colleagues, they observed that the absorption rate constant was not altered in malnutrition. This contrasts with work by Raghuram and colleagues indicating that tetracycline absorption was significantly reduced in subjects with malnutrition and pellagra but not in patients with vitamin B complex deficiency or in patients with severe anemia.<sup>32</sup>

## DISTRIBUTION

Only free, unbound drug molecules are pharmacologically active. Because the amount of serum protein changes over the first few years of life, the pharmacokinetics and pharmacodynamics of a drug may change. The important serum proteins that bind to drug molecules and biogenic amines and lipids include albumin, alpha 1-acid glycoprotein, sex-hormone-binding proteins, and lipoproteins. These changes in circulating plasma proteins can impact the distribution of highly bound drugs. In neonates and young infants, a reduction in total plasma proteins can result in the availability of active drug due to an increase in the free fraction of drug.<sup>3</sup> The serum concentration of alpha 1-acid glycoprotein is lower in children. On the other hand, the concentrations of certain fetal serum proteins are higher in infants and may lead to relatively unique pharmacokinetic changes in this population. For example, in neonates, the presence of fetal albumin is associated with reduced binding capacity to weak acids and, this, along with a corresponding increase in bilirubin and free fatty acids, resulting in a high free fraction of highly protein bound drugs such as phenytoin.<sup>3</sup>

Drugs can be distributed into various body compartments such as the intracellular fluids, extravascular space, lean body tissue, and adipose tissue. Alterations in body composition, particularly the presence of edema, can influence the plasma clearance of drug by changing the medication's volume of distribution.<sup>33</sup> Many medications, once in the systemic circulation, become bound to plasma protein, such as albumin, globulins, and lipoproteins. These binding proteins play an important role in the intravascular transport of the drugs to the target organs. In the bloodstream, drugs that are not bound to plasma proteins are free and are able to exert their pharmacologic response. Malnutrition can alter the rate of tissue protein synthesis as well as the concentration of plasma proteins. The extent of drug-protein binding depends on the concentration of plasma bind proteins as well as the physicochemical properties of the medication. In malnutrition, albumin and lipoprotein synthesis are reduced, whereas globulin and  $\alpha$ 1-acid glycoprotein synthesis are increased.<sup>19</sup> Drugs extensively bound to  $\alpha$ 1-acid glycoprotein, such as propranolol, have a decreased percentage of drug unbound in malnutrition, resulting in a lesser amount of active drug available to exert a therapeutic response. Other drugs, such as metronidazole, have no significant change in volume of distribution between malnourished and well-fed children.<sup>34</sup>

## METABOLISM

In chronic starvation, the body is able to adapt and alter various processes to protect or maintain enzyme activities.<sup>35</sup> In fact, in chronic starvation, enzyme activity may even increase. Endocrine tissue is typically affected in semistarvation as

many hormones serve as substrates for drug-metabolizing enzymes.<sup>36</sup> For example, elevations in free cortisol are often seen in malnutrition that may enhance the metabolism of contraceptive steroids in malnourished women, thus increasing the risk of contraceptive failure in that population.<sup>37</sup>

## CLEARANCE

Hepatic clearance of drugs may be affected by several major physiologic changes that occur during malnutrition. Protein deprivation or malnutrition may result in a reduction in cardiac function with a subsequent decreased perfusion of the liver and kidneys.<sup>38</sup> Typically, hepatic drug clearance is determined by three independent factors: hepatic blood flow, the amount of free fraction of the drug in blood, and hepatic clearance of the unbound drug. Diminished hepatic blood flow can reduce the clearance of drugs with high extraction ratios (ie, those in which hepatic clearance of the unbound drug depends on hepatic blood flow but not on changes in protein binding). Presystemic metabolism can become altered. Increases in the unbound fraction of a drug owing to hypoalbuminemia provide more available drug for metabolism, resulting in lower serum concentrations.<sup>38</sup>

The kidney is extensively involved in drug elimination. Renal elimination includes the processes of glomerular filtration, active tubular secretion, and passive tubular excretion. Drugs or their metabolites that are primarily filtered and excreted renally may be affected by nutritional status. Dietary protein increases renal blood flow, GFR, and renal tubular function.<sup>39</sup> Severe PEM is associated with decreased GFR and renal blood flow.<sup>40</sup> When renal perfusion is reduced, less drug is available to be filtered by the tubules. However, because plasma protein binding is also reduced, more free drug becomes available for renal excretion, thus further reducing plasma drug concentrations. Medications that have decreased renal elimination in severely malnourished patients include penicillins, tetracyclines, cefoxitin, aminoglycosides, and methotrexate.<sup>27</sup>

Refeeding an undernourished patient can often increase the systemic clearance of a medication, necessitating a dosage adjustment to maintain efficacy. For example, with theophylline, the volume of distribution decreases and the rate of elimination gradually increases in malnourished patients given a dextrose-based parenteral nutrition (PN) solution for at least 2 days.<sup>41</sup> The protein component of enteral or PN, however, appears to be the major macronutrient enhancing systemic clearance of affected drugs in patients transitioned from the "unfed" to the "fed" state. Lares-Asseff and associates confirmed these findings in their study investigating the pharmacokinetics of metronidazole in severely malnourished children.<sup>34</sup> Based on the clearance data, they recommended that the

daily maintenance doses for pediatric patients with severe malnutrition should be 60% less of the usual pediatric dose to achieve and maintain a therapeutic plasma concentration of metronidazole.

## DRUGS IN KWASHIORKOR

Kwashiorkor is associated with edema resulting from increases in total body water, extracellular fluid volume, and plasma volume along with a decrease in intracellular water.<sup>42</sup> Lares-Asseff and colleagues studied the effects of nutritional status of children with autoimmune disease on the disposition of acetylsalicylic acid and its metabolites.<sup>43</sup> They concluded that a decrease in the hydrolysis and oxidative reaction of the metabolic pathway of acetylsalicylic acid and its metabolites occurs in children with PEM with juvenile rheumatoid arthritis. This suggests that the hepatic elimination of salicylates may be altered by disorders of nutritional state.<sup>44</sup>

Based on these and other studies, it is thought that low protein intake results in a negative nitrogen balance that decreases drug metabolism, whereas drug metabolism in patients receiving adequate total calories but with less than optimal protein intake is not significantly impacted.<sup>45</sup>

## DRUGS IN MARASMUS

Unlike kwashiorkor, marasmus can be considered as an adaptation to an insufficient energy intake. There is decreased total body water, reduced intracellular water, increased extracellular fluid, and increased plasma volume.<sup>27</sup> Gentamicin, which distributes predominantly to extracellular fluids, has an increased volume of distribution in malnourished patients compared with well-nourished patients.<sup>46</sup> Antipyrine, a drug model commonly used as an index of hepatic drug-metabolizing capacity, distributes primarily in total body water and has been shown to have no variation in the apparent volume of distribution in malnourished children.<sup>47</sup> Likewise, in patients treated with metronidazole, a medication that also has a large volume of distribution, no difference in volume of distribution was observed between malnourished and nutritionally rehabilitated children.<sup>34</sup> A pharmacokinetic study by Treluyer and colleagues focused on the impact of human global PEM on quinine metabolism.<sup>48</sup> In that study, they reported that the metabolism of quinine is increased in children with global malnutrition, suggesting that the dosing interval in these children be reduced to obtain the same therapeutic quinine levels as seen in well-nourished children.

In summary, normal or increased drug metabolism occurs in mild to moderate cases of malnutrition, whereas decreased metabolism is seen in severe cases of malnutrition. Given the unique needs of the malnourished ill child special guidelines have been created for the use of antimicrobial agents.<sup>49</sup>

## OBESITY

Obesity (ie, BMI >95th percentile for age and sex) results in altered body composition in which there is both an increased proportion and absolute amount of adipose tissue as well as an increase in lean body mass, blood volume, cardiac output, and organ size.<sup>50</sup> In children, obesity can result in an expansion of blood volume, resulting in increased stroke volume and cardiac output. Increased abdominal fat can also lead to increased intraabdominal pressure and impact gastric emptying.<sup>51</sup> Drug distribution depends on body composition and may be altered in obese patients. Absorption of drugs evaluated to date appears to be unchanged owing to obesity; however, the data are very limited.<sup>52</sup> Severely obese patients who have undergone bariatric surgery for weight loss are more likely to experience altered drug absorption that may affect the clinical responses to therapy. Generally speaking, malabsorption of drugs is more likely to occur with the primary malabsorptive procedures such as jejunioileal bypass and pancreaticobiliary diversion. A commonly performed surgical procedure for weight loss is the Roux-en-Y gastric bypass, which is a primary restrictive procedure with mild malabsorptive component. The impact of Roux-en-Y gastric bypass on pharmacokinetics has not been investigated systematically.

The lipophilicity of a drug determines the extent to which obesity influences the volume of distribution and ultimately whether dosing should be based on actual or adjusted body weight. Highly lipophilic drugs, such as lidocaine, thiopental, phenytoin, verapamil, and most benzodiazepines, have an increased volume of distribution in severely obese patients.<sup>50</sup> Modest increases in volume of distribution have also been reported for aminoglycosides, heparin, ibuprofen, methylxanthines, prednisolone, and vancomycin, suggesting that an adjusted body weight rather than actual body weight (ABW) be used to avoid toxicity.<sup>52</sup> However, the most accurate approach to adjust for the excess body mass is unknown and appears to be different depending on the characteristics of individual compounds. Therapeutic drug monitoring is recommended when applicable to optimize therapy.

Although the protein binding of acidic drugs is unchanged, the free fraction of basic drugs may be decreased.<sup>52</sup> Similarly, changes in hepatic drug clearance are variable. Phase I reactions and phase I acetylation appear to be unaffected by obesity, but the phase II glucuronidation and sulfonation pathways are enhanced. Obesity may also affect systemic clearance of highly extracted drugs such as aminoglycosides and unmetabolized procainamide.<sup>52</sup> Both glomerular filtration and tubular secretion also appear to be increased.<sup>32</sup> Renal clearance of drug that mediated by both glomerular filtration and active secretion, such as digoxin and cimetidine, are relatively unchanged in obesity.<sup>52</sup>

Aminoglycosides are distributed within the extracellular fluid compartment. Early dosing recommendations suggested that initial dosing be based on ideal body weight (IBW) as it was thought that the drug distributed only into lean body mass. Schwartz and colleagues, however, have since determined that when the volume of distribution is corrected for total body weight, it is significantly smaller when compared with normal-weight subjects.<sup>53</sup> The distribution of aminoglycosides into excess body weight is estimated to be about 40% of that distributed into ideal body tissue. The authors concluded that initial dosing of aminoglycosides in obese patients be determined by adding 40% of the excess weight to the patient's IBW, with subsequent dosage adjustments based on serum drug levels and clinical status.

Example: For a 7-year-old child, 41 kg, 135 cm, gentamicin, 2.5 mg/kg/dose intravenously every 8 hours, is ordered:

1. Determine IBW<sup>14</sup>

$$IBW = \frac{ht^2 \times 1.65}{1000} = IBW \text{ kg, height cm}$$

$$IBW = \frac{135^2 \times 1.65}{1000} = 30 \text{ kg}$$

2. Determine dosing weight (DW): DW = IBW + (ABW - IBW) × 0.4 DW is in kg, ABW is in kg

$$DW = 30 \text{ kg} + (41 - 30) \times 0.4 DW = 34.4 \text{ kg}$$

3. Calculate gentamicin dose using DW: mg/kg/dose × DW = dose in mg 2.5 mg/kg/dose × 34.4 kg = 86 mg intravenously every 8 hours

A similar controversy exists for optimizing theophylline dosing in obese patients and whether actual or IBW should be used to calculate the initial theophylline loading dose. This is attributable to conflicting data suggesting that variations in distribution volume may be the result of differences in the degrees of obesity within study populations.<sup>55</sup> Visram and colleagues suggested that the differences in theophylline volume of distribution based on IBW and ABW increases as the degree of obesity increases.<sup>55</sup> They recommended that theophylline dosing in patients with mild to moderate obesity be based on ABW but that IBW be used when initiating therapy in severely or morbidly obese patients.

Hepatic drug metabolism may also be altered in patients with nonalcoholic steatohepatitis (NASH),<sup>34</sup> including enhanced glucuronidation and sulfonation, causing a faster drug excretion compared with normal-weight subjects.<sup>52</sup> CYP2E1 expression and activities are increased in obese patients with nonalcoholic fatty liver disease, including NASH.<sup>56</sup> Compounds that are metabolized by CYP2E1 include fatty acids, ketones, and ethanol. It appears that the presence of an increase amount of fatty acids, such as in the case of NASH, leads to an induction of this enzyme. The metabolic pathways of fatty acids and other xenobiotics may lead to the release of free radicals, which can cause lipid peroxidation

and liver injury, including mitochondrial damage. These changes are partially responsible for the hepatic inflammation and fibrosis sometimes observed in patients with NASH.<sup>57</sup> Patients with fatty liver may also be more susceptible to the toxic effects of drugs owing to impaired metabolism.<sup>58</sup>

## EFFECT OF DIETARY MANIPULATION ON DRUG KINETICS

Several dietary factors can alter the rate of drug metabolism. Model drugs, such as antipyrine, theophylline, and acetaminophen, have often been used in these studies. Both food and fluids can alter the rate and extent of drug absorption. These alternations in response may occur as a result of influences on gastric pH, gastric emptying time, intestinal motility, and mesenteric and hepatic portal blood flow or biliary flow, or the activities of the enzymes and transport proteins in the gut.<sup>59</sup> Direct physicochemical interactions with dietary components can also alter the absorption of susceptible agents.<sup>60</sup> Interactions such as the binding of the medication with metal ions, solubilization of the drug in dietary fat, or adsorption of the drug to insoluble dietary components may occur.<sup>61</sup>

Dietary changes can alter the expression and activity of hepatic drug-metabolizing enzymes.<sup>62</sup> This can lead to alteration in the systemic elimination kinetics of medications metabolized by these enzymes; however, the impact of this change is typically minimal.<sup>62</sup> The rate of drug metabolism can be accelerated by drugs themselves or by a variety of dietary factors, such as protein supplementation or inclusion of cruciferous vegetables or charcoal-broiled meats in the diet.<sup>63</sup> It has also been reported that charcoal-broiled beef induces the metabolism of antipyrine and theophylline, reducing the half-lives of these drugs by 20%.<sup>64</sup> These effects were related to hepatic enzymatic induction caused by charcoal-broiled beef that contains large quantities of polycyclic aromatic hydrocarbons (PAHs).<sup>65</sup> PAHs are potent inducers of CYP1A2, the primary metabolizing enzyme for theophylline and antipyrine. Conversely, low-protein, high-carbohydrate diets, and various vitamin and mineral deficiencies can reduce levels of drug-metabolizing enzymes and consequently the rate of drug metabolism so that the serum drug concentrations decline much more slowly, resulting in increased drug potency.<sup>63</sup>

In general, when orally administered medications are taken with meals, the rate rather than the extent of absorption is more significantly affected. Food affects drug absorption by enhancing gastric blood flow in conjunction with delayed gastric emptying. Food can increase, decrease, or have no effect on the absolute systemic availability of a medication.<sup>66</sup> Concomitant food ingestion reduces the absorption of drugs such as ampicillin, penicillin, and isoniazid.<sup>27</sup> Conversely, food may actually enhance the absorption of other

**Table 2 Medications Whose Absorption Is Affected by Food**

Drug Absorption Reduced/Delayed by Food	Drug Absorption Enhanced by Food
Ampicillin	Atovaquone
Aspirin	Carbamazepine
Atenolol	Chlorothiazide
Azithromycin	Cefuroxime
Captopril	Clofazimine
Cefaclor	Diazepam
Cefixime	Erythromycin estolate
Cephalexin	Erythromycin ethyl succinate
Ciprofloxacin	Ganciclovir
Didanosine	Griseofulvin
Doxycycline	Hydralazine
Dirithromycin	Hydrochlorothiazide
Erythromycin stearate	Itraconazole
Famciclovir	Ketoconazole
Indinavir	Lithium
Isoniazid	Lovastatin
Loratidine	Methylphenidate
Nafcillin	Metoprolol
Penicillin G or V	Nelfinavir
Phenobarbital	Nitrofurantoin
Phenytoin	Propranolol
Rifampin	Propoxyphene
Sucralfate	Ritonavir
Tetracycline	Saquinavir
Thioridazine	Spironolactone
Zafirlukast	

Adapted from reference 67.

medications, including diazepam, lithium, carbamazepine, and griseofulvin. Table 2 lists medications whose absorption is altered by food. In most cases, changing the rate of absorption of a drug alone without affecting the total amount absorbed should not affect its efficacy.

The composition of the meal will alter splanchnic blood flow. Blood flow can be doubled by a high-protein liquid meal and slightly reduced by a liquid glucose meal.<sup>68</sup> The significance of this effect on splanchnic flow is important for those medications with high hepatic extraction.<sup>61</sup> Continued meal intake, especially food with high fat content, will also slow the rate of gastric emptying, which may subsequently cause a delay in drug absorption from the GI tract. Changes in gastric emptying are related not only to the physicochemical properties of the drug but also to the type of meal itself. Hot meals, highly viscous solutions, or those rich in fat have the most significant affect in slowing down gut motility.<sup>61</sup> Melander and colleagues reviewed the impact of food on the presystemic clearance of drugs.<sup>69</sup> They observed that meals commonly enhanced presystemic clearance of lipophilic basic drugs (eg, propranolol, amitriptyline) but rarely altered the clearance of drugs that were lipophilic acids (eg, salicylic acid, penicillin). Alternatively, food may reduce presystemic clearance of some lipophilic basic drugs via transient, complex effects on splanchnic-hepatic blood flow. Furthermore, repeated intake of specific nutrients (eg, protein) and food contaminants (eg, benzopyrene) can

enhance presystemic drug clearance by enzyme induction.

In some instances, dietary manipulation can act as a therapeutic strategy. Nutt and colleagues reported that large neutral amino acids and the medication levodopa compete for transport from the plasma to the brain and may be partly responsible for the “on-off” phenomenon often seen in patients treated with levodopa for Parkinson’s disease.<sup>70</sup> By reducing protein intake, patients who failed to respond to a dosage adjustment in their levodopa may see clinical improvement.

### IMPACT OF SPECIFIC NUTRIENTS ON DRUG KINETICS

Until recently, most practitioners dismissed the possibility that dietary substances could significantly alter medication response by affecting intestinal transporter and metabolizing enzymes. This is based on the commonly believed misconception that the absorption of most drugs is a passive process and that the role of the intestine in drug elimination is minimal.<sup>62</sup> Since the report of the interaction between grapefruit juice and several medications was described, this premise has changed, and the role of the diet on drug performance is being reevaluated.<sup>71</sup>

### CARBOHYDRATES

The impact of carbohydrates on drug metabolism is conflicting. It is known that high-carbohydrate diets may induce the expression of several glycolytic and lipogenic hepatic enzymes,<sup>72</sup> but some suggest that carbohydrates have little impact on drug metabolism.<sup>73</sup> Kappas and colleagues, however, noted that antipyrine and theophylline metabolism decreased in carbohydrate-supplemented diets but increased in the protein-enriched diet, suggesting that carbohydrates and protein have opposite effects on oxidative drug metabolism.<sup>63</sup> Although many medications are often given to children in a sugar syrup, little research has been done on its effect on disposition and action. Animal studies by Sonawane and colleagues suggested that dietary carbohydrates and fat may significantly influence the hepatic drug-metabolizing enzymes.<sup>74</sup> It has been hypothesized that these changes may occur owing to alteration in the phospholipid composition of endoplasmic reticulum or by limiting the supply of cofactor(s) necessary for optimal functioning of CYP and UGT.

### PROTEIN

Several investigators have reported that medications that undergo extensive first-pass effect, such as propranolol, metoprolol, and lidocaine, can have enhanced bioavailability after a high-protein meal owing to enhanced hepatic blood flow. High-extraction drugs can then rapidly pass through the liver, allowing higher drug concentrations in the systemic circulation.<sup>62,69</sup>

A decrease in dietary protein depresses creatinine clearance and renal plasma flow.<sup>75</sup> Specific dietary proteins can also impact a response to a medication. One of the classic examples is that of the monoamine oxidase inhibitor (MAO-I) drug class and the amino acid tyramine that is contained in aged cheeses, pickled/smoked meats, fermented foods, and red wines. Tyramine is an indirect sympathomimetic amine that releases norepinephrine from the adrenergic neurons, causing a significant pressor response. Typically, tyramine is metabolized by the enzyme monoamine oxidase before any significant increases in blood pressure are seen. If the enzyme is blocked, however, severe and potentially fatal rises in blood pressure can occur when tyramine-rich foods are ingested. Although MAO-Is are not used routinely as antidepressants, other medications, such as the oxazolidinone antibiotic, linezolid, also have MAO-I properties and patients should avoid ingesting large amounts of tyramine while being treated with this antibiotic.<sup>76</sup>

Dietary protein also affects the renal tubular transport of certain compounds, although the mechanism by which this occurs is still not understood. The binding of dietary proteins to a drug may underscore changes in bioavailability after a protein meal. For example increases in both the maximum concentration (C<sub>max</sub>) and area under the curve (AUC) are seen in patients receiving gabapentin. This enhanced absorption was attributed to trans-simulation, a carrier-mediated process in which increased intestinal luminal amino acid concentrations result in an upregulation and/or increased activity of the L-amino acid transporter.<sup>77</sup>

### DIETARY FAT

Lipids are an essential part of cell membrane structure and are involved in many of the normal enzymatic activities located within the cell membrane.<sup>73</sup> Diets that are deficient in fat or essential fatty acids decrease the activity of the enzyme systems responsible for the metabolism of nutrients.<sup>78</sup> Plasma free fatty acid levels become elevated after consumption of a high-fat meal, increasing the potential to become bound to plasma albumin, and subsequently displace albumin bound drugs, increasing the risk of drug toxicity.<sup>73</sup> Dietary fats along with food-stimulated secretions (eg, bile salts) may facilitate the solubilization and dispersion of lipophilic compounds. This may contribute to a reduction in the extent of first pass metabolism due to enhanced splanchnic blood flow.<sup>79</sup> Ingestion of diets high in fat has been associated with the induction of CYP2E1. The extent to which this enzyme is upregulated is dependent upon the type of fat. Polyunsaturated fats such as corn and menhaden oils appear to have the greatest influence in comparison to lard or olive oils. This can result in enhanced peroxidation of the polyunsaturated fatty acid substrates and contribute to free radical production.<sup>80</sup> The rate of gastric emptying is also

influenced by the fat content of a meal. Fat retards gastric emptying to a greater degree than does protein or carbohydrate.<sup>81</sup>

The effect of dietary fat on drug absorption, however, depends upon the route of the drug absorption, either portal or lymphatic. For medications absorbed via the lymphatic route, dietary fat enhances the absorption of the dissolved drug, whereas poorly bioavailable lipophilic drugs absorbed by the portal route have their absorption enhanced by improved drug dissolution. Conversely, lipophilic medications that have good bioavailability will less likely to be impacted by a high-fat meal. Moreover, hydrophilic medications are not impacted significantly when coadministered with fatty meals.<sup>82</sup>

The impact of food on the absorption of cyclosporine is controversial. There are conflicting reports stating that food impairs, enhances, or does not affect cyclosporine compared with the fasting state.<sup>83</sup> Similarly, high-fat meals may affect sirolimus bioavailability. When taken with a high-fat meal, the rate of sirolimus absorption is slower and results in a greater AUC in comparison to when taken in the fasted state. This contrasts with tacrolimus in which a 71% mean decrease in C<sub>max</sub> and a 39% mean decrease in AUC was seen immediately following its administration after a high-fat meal relative to when the same dose was given in the fasted state.<sup>84</sup>

The antiviral agent zidovudine is also impacted by dietary fat. When administered orally, its absorption is reduced when the drug is taken with a high-fat meal in comparison with when taken in the fasted state.<sup>85</sup> It is recommended that zidovudine be taken on an empty stomach to achieve peak serum concentrations.

## MINERALS

In most instances, mineral deficiencies (ie, zinc, iodine, magnesium, and potassium) have been associated with a decrease in drug oxidation and drug clearance.<sup>86</sup> Low dietary intake of iron, however, has been associated with an increase in some mixed function oxidase system (MFOs) functions and a decrease in other degradative activities, the reasons for which are not fully apparent.

## VEGETABLES

Diets rich in vegetables and fruit may also impact the response to medications. Both serve as sources of trace minerals that are contained in metalloenzymes, including several antioxidants. Many plants contain flavonoids, isothiocyanates, and allyl sulfides that are potent modulators of the cytochrome monooxygenase system.<sup>87</sup>

Phytochemicals are linked with the modulation of a variety of metabolic pathways. The most frequently sources include cruciferous vegetables, citrus juices, and spices. Dietary supplements and herbs are also associated with this category. There are five major families of phytochemicals: carotenoids (eg, beta carotene,

lycopene), alkaloids, phenolics (include flavonoids, coumarins, tannins), nitrogen compounds, and sulfur compounds (eg, isothiocyanates, allylic sulfur).<sup>88</sup> Recent research has focused on how vegetables and fruits can influence a variety of enzymatic pathways. Typically induction of these enzyme systems is rapid and plateaus within 5 days of continued daily ingestions of the food with the enzyme inducing capacity.<sup>88</sup>

Cruciferous vegetables, including brussels sprouts, cabbage, turnips, broccoli, cauliflower, and spinach, contain indols that induce aryl-hydrocarbon hydroxylase enzyme activity as well as the conjugation of phenacetin and acetaminophen.<sup>89,90</sup> In one study, patients fed a diet of brussels sprouts and cabbage had a 50% lower serum phenacetin level in comparison with the same subjects fed a control diet that contained none of the enzyme-inducing vegetables.<sup>90</sup> A later study investigated the effects of cruciferous vegetables on acetaminophen conjugation.<sup>89</sup> The researchers found that the test diet of cruciferous vegetables enhanced acetaminophen glucuronide conjugation as evidenced by a 16% decrease in the AUC, a 17% increase in metabolic clearance, and an increased plasma acetaminophen glucuronide-to-acetaminophen ratio.

Cruciferous vegetables are not the only plants that can impact drug response. Potatoes, tomatoes, and eggplant contain natural insecticide compounds called solanaceous glycoalkaloids that even in small amounts may greatly slow the metabolism of muscle relaxants and anesthetic agents such as suxamethonium, mivacurium, and cocaine. Cooking does not reduce them and they may remain in the body for several days after ingestion. Solanaceous glycoalkaloids inhibit butyryl cholinesterase, which breaks down many anesthetic agents, and cetylcholinesterase, which breaks down acetylcholine. When these enzymes are inhibited, patients receiving medications metabolized by them may take longer to recover from anesthesia.<sup>91</sup>

## GRAPEFRUIT JUICE AND DRUG INTERACTIONS

Bailey and his colleagues discovered that grapefruit juice, which was used as a taste-masking agent for alcohol, caused a two- to threefold increase in oral absorption of the calcium channel blocker felodipine.<sup>92</sup> This finding has subsequently led to the intensive investigation of grapefruit juice and drug interactions. This interaction is the classic example of drug–nutrient interaction exclusively caused by inhibition of intestinal CYP3A4. Oral absorption pharmacokinetic studies of CYP3A4 substrates, such as cyclosporine or felodipine, consistently showed that grapefruit juice increased the oral bioavailability of these agents. Interestingly, the plasma half-lives of most of the drugs studied were not affected, suggesting that the systemic clearance or hepatic metabolism of these drugs was unchanged by grapefruit juice. It was later

determined that this interaction occurs in the enterocytes but not in the hepatocytes. Furthermore, Lown and his colleagues showed that repeated consumption of grapefruit juice inhibits not only the intestinal CYP3A4 activity but also the expression of this gene in the enterocytes.<sup>10</sup> As grapefruit juice inhibits intestinal CYP3A4 expression and thus decreases the presystemic metabolism of certain drugs, the bioavailability of the affected agents will remain increased until the expression of the CYP3A4 gene returns to baseline. This suggests that mere separation of the administration time between grapefruit juice and the potential interacting drugs cannot prevent this interaction. Rather than reduce the dose of the affected drugs to avoid toxicity, patients should be advised to avoid grapefruit juice. In some centers, grapefruit juice has been removed from the institutional formulary to minimize the risk of this interaction.

## HIGH-FIBER DIETS

Dietary fiber and other bulk-forming compounds may interfere with the GI absorption of a medication.<sup>93</sup> The bioavailability of digoxin is reduced significantly when given with a fiber-rich meal, with almost half of the dose sequestered in or bound to the fiber.<sup>94</sup> Similar effects have been reported with lithium salts and lovastatin.<sup>95</sup> Stewart reported that several patients with recurrent major depression who had been successfully treated with tricyclic antidepressants became refractory to treatment after beginning a high-fiber diet.<sup>96</sup> Nutrient absorption can also be negatively impacted in the presence of a high-fiber diet. Zinc absorption in the intestine is reduced by the binding of zinc to a number of materials, including phytate, which is found in high-fiber diets.<sup>97</sup>

## COOKING METHODS

Drug metabolism can also be enhanced by the ingestion of charcoal-broiled beef. Patients fed such a diet saw a significant drop in serum phenacetin levels in comparison to the same subjects fed a control diet. It has also been reported that charcoal-broiled beef induced the metabolism of antipyrine and theophylline, reducing the half-lives of these drugs by 20%.<sup>98</sup> It has been postulated that these effects were related to the large quantities PAHs present in charcoal-broiled beef.

## VEGETARIANISM

Drug metabolism among vegetarians will vary dramatically depending on the protein intake. Most research has focused on Asian vegetarians in which the half-lives of drugs that underwent significant hepatic metabolism (antipyrine, acetaminophen, phenacetin) were significantly longer than in nonvegetarians.<sup>99</sup> When similar studies were conducted in white vegetarians, they found

no significant difference in half-life between the vegetarians and nonvegetarians.<sup>100</sup> Protein quality may contribute to these findings as the authors found that protein intake between the white vegetarians and the nonvegetarians was similar.

Vegetarian diets are also associated with lower circulating concentrations of sex steroids hormones, increased fecal excretion of estrogens and different hormonal profiles in comparison to individuals consuming an omnivorous diet.<sup>101</sup> Vegetable intake may influence total body estrogen load via the modulation of CYP enzymes involved in estrogen metabolism. CYP13C, found in cruciferous vegetables, can increase estrogen hydroxylation.<sup>102</sup>

### VERY LOW CALORIE DIETS

In diets involving severe protein-energy restriction, such as extreme slimming diets, the metabolism of drugs may be affected in one of two ways. First, tissue protein is catabolized and used as an energy source, thus reducing the availability of amino acids for protein synthesis, which in turn reduces the amount of enzymes available for drug metabolism. Second, endogenous substrates derived from carbohydrate and protein such as glucuronide, sulfate, and glycine could also compete for the tissue needs for these nutrients and that of the drug metabolism/detoxification.<sup>103</sup> Eating habits, especially among dieters that omits or severely restrict whole categories of foods, have a negative impact on micronutrient status. Diets that eliminate all animal foods provide almost no cyanocobalamin and have been associated with other vitamin deficiencies including vitamin C. Moreover, skipping meals and fad diets to lose weight frequently compromise micronutrient intake. It should be routinely assumed that it is extremely difficult to meet all the requirements at intakes of less than 1,200 calories per day. An analysis of 11 published weight loss diets showed that none provided 100% of the US recommended dietary allowance for representative vitamins.<sup>103</sup>

In a review by Anderson, the author suggests that the metabolic improvements seen after obese patients receive very low calorie diets are not different from those obtained by equally large weight losses promoted by other methods.<sup>104</sup> Patients with very low calorie diet weight loss have improved hyperinsulinism as a result of a reduction in basal insulin production as well as enhanced hepatic insulin extraction. Moreover, it is thought the weight loss through very low calorie diet lowers the hepatic glucuronidation of drugs leading to higher plasma concentrations of the affected drugs.<sup>105</sup> Despite this, however, the fatty liver may still be more susceptible to drug toxicity.<sup>106</sup> For example, several reports in have suggested that caloric restriction may contribute to acetaminophen hepatotoxicity by altering drug metabolism although under controlled conditions, Schenker and colleagues so no impact on food restriction of acetaminophen metabolism.<sup>107</sup>

### OTHER DIETARY RESTRICTIONS

In addition to caloric restriction, restriction of other dietary components can also impact drug response. In patients who have sodium restricted diets, there is an increased risk of acute renal failure if these same patients are given concomitant angiotensin-converting enzyme inhibitors or non-steroidal antiinflammatory agents. There is enhanced nephrotoxicity in patients who are sodium depleted and are given cyclosporine or tacrolimus. Sodium restriction can also increase the renal tubular absorption of lithium, leading to toxicity. Patients receiving aminoglycosides, amphotericin, cisplatin, or radiocontrast media in conjunction with a low-sodium diet have an increased risk for hemodynamic nephrotoxic and ischemic acute renal failure. For reasons still not known, the efficacy of calcium channel blockers is reduced in patients on a sodium-restricted diet.<sup>108</sup>

### IMPACT OF BEVERAGE TYPE ON DRUG BIOAVAILABILITY

To most practitioners, the term beverage refers to any drinkable liquid other than plain water. They are typically classified as caffeinated, alcoholic, milk-based, mineral waters, or fruit/vegetables juices.<sup>109</sup> Depending upon the type of fluid taken with a medication, drug absorption may be affected. Mixing drugs with fruit juices or other beverages to mask their taste may impact absorption due to changes in gastric pH. Dairy products decrease the absorption of tetracyclines and reduce their bioavailability due to the formation of insoluble chelates between the drug and the calcium present in the beverage. Similar decreases in bioavailability were noted when fluoride tablets are taken with milk. Tannins present in teas may impair iron absorption. Alcoholic beverages reduce the absorption of folic acid, cyanocobalamin, and magnesium. Soft drinks, such as colas, may decrease drug absorption for a variety of reasons. The phosphoric acid and sugar present in these drinks can slow gastric emptying and the tendency to serve them chilled may also reduce the rate of blood flow within the intestines. Moreover, the carbonation may increase mixing and possibly motility. Interestingly, the acidic pH of cola beverages can be used to optimize clinical responses of both ketoconazole and itraconazole in patients with gastric hypochlorhydria, such those patients with AIDS gastropathy.<sup>109</sup> The effects of grapefruit juice on drug disposition are discussed separately.

### PARENTERAL NUTRITION

Lack of oral nutrient intake during PN leads to mucosal atrophy of the bowel along with a reduction in gastric biliary, pancreatic, and intestinal secretions.<sup>110</sup> Bacterial overgrowth can result in a progressive decline in intestinal function owing to impaired motility and depressed enzyme activity. This may alter the rate and extent of

absorption of specific nutrients as well as various drugs. Decreases in nutrient absorption include fat, iron, peptides, and vitamins A and B<sub>12</sub> as well as drugs such as chloramphenicol, chloroquine, tetracycline, and rifampin.<sup>38</sup>

PN has been observed to decrease hepatic drug and xenobiotic metabolism in animals and humans.<sup>111,112</sup> Drug metabolism may be altered due to jejunal and ileal mucosal hypoplasia and hypofunction as parenterally administered nutrients bypass the intestine. Studies using antipyrine as a marker have shown that PN regimens containing amino acids have higher antipyrine clearance than regimens consisting mainly of dextrose.<sup>111</sup> Burgess and colleagues investigated the response of PN regimens on antipyrine clearance.<sup>112</sup> Patients receiving a postoperative 2,000 kcal PN regimen providing all nonprotein calories as dextrose showed a 34% reduction of mean antipyrine clearance after 7 days of total parenteral nutrition compared with unfed controls. This effect was seen also in patients receiving a 1,600 kcal dextrose-based regimen. Moreover, patients receiving a 2,000 kcal PN regimen in which 500 kcal were provided as lipid, mean antipyrine clearance was not significantly different from that of the unfed control group. This study suggested that hepatic CYP1A activity might be affected by different total parenteral nutrition regimens.

### EFFECTS OF DRUGS ON NUTRIENT STATUS

Drugs can alter the use of many nutrients by a variety of mechanisms, both specific and nonspecific. Malabsorption syndromes may occur from direct toxic effects of the medication to the intestinal mucosa, inhibition of enzymes, binding of bile and fatty acids, alteration of dietary ions, or alteration of GI pH. Indirect, nonspecific effects of a drug may manifest themselves as a decrease in appetite, ultimately leading to a decrease in food intake.

Although the concept of drug–nutrient interactions is not a new one, only recently has it reached the forefront in the medical world. Malnutrition, as well as the composition of the diet, can affect the disposition of a medication's half-life.<sup>113</sup> In addition to traditional dietary components, nonnutrient ingredients, such as food additives, preservatives, antioxidants, sweeteners, flavoring, and coloring agents, can interact with a medication. Natural products, such as plant food groups, contain alkaloids, flavonoids, and other compounds; can behave in the body in the same manner that a drug would; and, consequently, can be involved in a variety of interactions and are potentially toxic if they are consumed or accumulate in the body.<sup>114</sup> Drug–nutrient interactions are typically defined as situations that result from chemical, physical, physiologic, or pathophysiologic relationships between nutrients and drugs.<sup>115</sup> Infants and adolescents, like the elderly, are at particular risk

for drug–nutrient interactions. Several factors may influence the possible interactions: first, their nutrient needs are typically higher; second, the systems for detoxification of nutrients may be incomplete; and third, adolescents (especially females) tend to restrict their diets and thus are unable to meet the actual recommended intakes for a variety of micronutrients.<sup>116</sup> Furthermore, the minimum dietary requirement may be insufficient when a patient is under psychological and pathologic stresses, as in the case of pregnancy or athletic training. In pathologic states, the requirement for some micronutrients may be increased.

Drugs may potentially cause vitamin deficiency ranging from subclinical deficiency to clinical intensity of the interaction may in many cases depend on the nutritional status of the patient. Patients with borderline intake of vitamins or those in poor nutritional health appear to be at greater risk of developing symptomatic vitamin deficiency states. Other factors include the type of drug treatment, dose, and duration of therapy, as well as the age of the patient. For example, individuals on a normal diet rarely become vitamin K deficient, although malnourished patients, regardless of cause, often have moderate or significant deficiency, often with prolonged bleeding times.<sup>116,117</sup> Cohen and colleagues reported that hospitalized patients may become vitamin K deficient within 7 to 10 days after admission, with those at greatest risk being those who were previously malnourished and had received antibiotics for seven or more days.<sup>118</sup> Adolescents, due to periods of rapid growth, are particularly sensitive to micronutrient status. Even a typical diet may not meet their high nutrient demands necessary for growth. Intake of folate and vitamin A tend to be less than optimal.<sup>103</sup>

## ABSORPTION OF NUTRIENTS

There are also many secondary mechanisms that can interfere with nutrient absorption. Medications may alter gastric or intestinal secretion, pancreatic exocrine function, or hepatic bile secretion. For example, H<sub>2</sub> antagonists and proton pump inhibitors inhibit gastric acid production. Chronic use of these medications can significantly decrease the absorption of vitamin B<sub>12</sub>.<sup>116</sup>

The direct systemic effect of a drug on one nutrient may have secondary effects on another nutrient. Isoniazid and cimetidine inhibit the hydroxylation of vitamin D in the liver and kidney, and phenytoin and phenobarbital promote the breakdown of vitamin D metabolites, each resulting in a functional deficiency of vitamin D and secondary impairment of calcium absorption.<sup>119</sup> Neomycin, colchicine, and para-aminosalicylic acid may damage intestinal mucosa and destroy intestinal villi and microvilli, resulting in an inhibition of brush border enzymes and intestinal transport systems.<sup>120</sup> Nonsteroidal anti-inflammatory agents can cause multiple small hemorrhages of the intestinal mucosa leading to iron deficiency anemia and decreased absorption of vitamin C.<sup>121</sup> Folic acid deficiency and macrocytic anemia can occur

in patients on chronic aspirin therapy, especially if their diet is low in dietary sources of folate.<sup>94</sup>

Laxative abuse has also been implicated with malabsorption of vitamin D and calcium. Use of irritant laxatives, such as phenolphthalein and bisacodyl, may damage intestinal epithelial cells and impair colonic reabsorption, resulting in steatorrhea, protein-losing enteropathy, and decreased absorption of glucose, potassium, calcium, and vitamin D.<sup>122</sup> Other stool regimen medications, such as docusate, alter electrolyte transport and can cause hypomagnesemia owing to GI losses and failure of colonic reabsorption.<sup>123</sup> Orally ingested mineral oil can coat ingested food particles along with the surface of the intestines. This forms a mechanical barrier to the digestion and absorption of nutrients. Mineral oil also increases gastric motility, which reduces the time required to adequately absorb ingested nutrients.<sup>124</sup> Furthermore, studies have shown that mineral oil, especially when taken at mealtime or during the postprandial absorptive period of optimal nutrient absorption, can reduce the absorption of vitamin D.<sup>124</sup>

Alterations in vitamin and mineral absorption can also occur owing to chelation or precipitation with a medication. Cholestyramine, a basic anion-exchange resin, binds bile salts and impairs the absorption of fat-soluble vitamins, vitamin B<sub>12</sub>, folic acid, and the minerals calcium, iron, and zinc.<sup>125</sup> Aluminum hydroxide and magnesium hydroxide-containing antacids may form nonabsorbable phosphates in the gut lumen, resulting in hypophosphatemia along with anorexia and secondary syndromes of hypomagnesemia and osteomalacia.<sup>119</sup>

Alteration in GI pH may also cause drug-induced malabsorption. Drugs that increase gastric pH (eg, H<sub>2</sub> antagonists) can also decrease the breakdown of fat necessary to complex with calcium, thus reducing gut absorption.<sup>126</sup> Antacids can also reduce the bioavailability of riboflavin and folic acid as well as copper and iron, all of which depend on a low pH.<sup>127</sup> In some cases, the effect of drugs on nutrient malabsorption may be indirect. Proton-pump inhibitors (eg, omeprazole, lansoprazole) suppress gastric acid release and induce a mild achlohydric state. The decrease in gastric pH leads to reduces the amount of cobalamin liberated from diet. This, in turn, limits the binding of cobalamin to intrinsic factor. Chronic use of this class of drugs may lead to malabsorption of cobalamin in some patients. Vitamin supplementation may be necessary to minimize the risk of developing anemia.<sup>128</sup>

## METABOLISM OF NUTRIENTS

Drugs may affect nutrient metabolism by several methods. They may inhibit the essential intermediary metabolism of a nutrient, usually a vitamin, or promote the catabolism of the nutrient. Medications with these properties may be used therapeutically, as in the case of coumarin anticoagulants or methotrexate. In other cases,

this may be an unwanted side effect, as in the case of pyridoxine antagonism seen in isoniazid and hydralazine use. Isoniazid and hydralazine can result in pyridoxine deficiency by the inhibition of pyridoxal kinase. Both compounds deplete pyridoxine stores and consequently the neurotransmitter gamma-aminobutyric acid, resulting in seizures. Administration of pyridoxine in cases of isoniazid overdose eliminates seizures and metabolic acidosis, which often occur.<sup>129</sup>

Many medications induce drug metabolism enzymes. This results in greater activity of these enzymes, increasing the demand for their vitamin cofactor, and, with chronic drug therapy and marginal nutrient intakes, can precipitate signs of deficiency of several vitamins, especially folic acid. Triamterene can inhibit dihydrofolate reductase, resulting in megaloblastosis.<sup>130</sup> The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor class of antihyperlipidemic agents (ie, statins) can lower plasma concentration of endogenous ubiquinone (coenzyme Q), a cellular antioxidant.<sup>131</sup>

Patients receiving chronic anticonvulsant therapy are at particular risk of developing metabolic bone disease as a result of these types of reactions.<sup>132</sup> Several mechanisms have been suggested. One suggests that drugs such as phenytoin, a microsomal enzyme inducer, stimulate the catabolism of vitamin D to produce an inactive metabolite.<sup>133</sup> Another theory suggests that phenytoin, alone or in combination with phenobarbital, interferes with vitamin K metabolism, with a corresponding elevation in serum osteocalcin levels without  $\alpha$ -carboxylglutamate (Gla) residues, resulting in metabolic bone disease because osteocalcin-containing Gla residue is necessary for normal bone mineralization.<sup>134</sup>

Patients treated with cephalosporin antibiotics may develop hemorrhagic states owing to drug-induced vitamin K deficiency.<sup>135</sup> It is thought that these antibiotics block the vitamin K reductase, which is necessary for vitamin K activation.<sup>136</sup> They may also block carboxylation of vitamin K-dependent peptides to yield Gla residues that are required for calcium binding in the conversion of vitamin K-dependent proenzymes to their active state, which are needed in the coagulation cascade.<sup>136</sup>

Some drugs have been linked with subnormal serum folate levels, probably owing to weakly bound folate to serum proteins that can be easily displaced by drugs.<sup>137</sup> The mechanism for this interaction has yet to be described, but it appears that there is a decrease in serum binding of methyltetrahydrofolate caused by the drug itself or one of its metabolites.<sup>138</sup>

Folate deficiency secondary to long-term phenytoin therapy is a common occurrence; approximately 75% of patients taking anticonvulsants have low serum folic acid levels.<sup>139</sup> Progression to megaloblastic anemia is relatively rare, however.<sup>140</sup> Supplementation of folic acid with as little as 1 mg/d may lead to a significant decrease in serum phenytoin concentrations in 15 to 50% of the patients.<sup>141</sup> Although the exact mechanism is unknown, pharmacokinetic analysis of phenytoin

suggests that folic acid may increase the affinity of the metabolic enzyme(s) involved in the elimination of the phenytoin without causing overall enzymatic induction.<sup>141,142</sup> To avoid potential folate deficiency and subsequent fluctuations in serum phenytoin levels, practitioners should routinely supplement all patients with folate when phenytoin therapy is initiated.<sup>141</sup>

Like phenytoin, sulfasalazine, an anti-inflammatory agent used to treat Crohn's disease and juvenile rheumatoid arthritis, is one of the leading causes of drug-induced folate deficiency in children.<sup>142</sup> Megaloblastic anemia, caused by folate deficiency, has been reported in patients receiving high doses of sulfasalazine for prolonged periods.<sup>143</sup>

Aspirin has also been linked with folate deficiency. Serum folate levels are known to be low in many patients with rheumatoid arthritis.<sup>116</sup> It is thought that aspirin alters the transport of folate by competing for binding sites on serum proteins.

Methotrexate, a chemotherapeutic agent that is also used to treat psoriasis, rheumatoid arthritis, and Crohn's disease, limits the availability of methyl groups derived from one-carbon metabolism by inhibiting competitively a key enzyme in the intracellular folate metabolism.<sup>144</sup> Methotrexate functions as an antimetabolite, reversibly inhibiting dihydrofolatereductase.

Valproic acid (VPA), an antiepileptic agent, has been associated with folate deficiency. Like other agents, the mechanism is not fully understood; however, it is thought that VPA causes an alteration in the methionine cycle.<sup>145</sup> This results in an elevation of tetrahydrofolate levels and a reduction of both formulated forms of folate. This could also explain VPA's role as a teratogen.<sup>146</sup> In addition, it has been established that VPA may induce L-carnitine deficiency. Patients who develop VPA-induced carnitine deficiency typically experience hyperammonemia syndrome with no other abnormality in the liver function tests. If diagnosed early, the clinical presentation, which includes altered mental status or encephalopathy, can be reversed by L-carnitine supplementation.<sup>147</sup>

## DRUG EFFECTS ON NUTRIENT TRANSPORT

There are several mechanisms by which a drug can impact nutrient transport and then lead to nutritional deficiency. A nutrient can become displaced from plasma protein binding sites by a medication, leading to an increase in the renal excretion of the nutrient, or a drug may compete with a nutrient such that intracellular use of the nutrient is impaired.<sup>148</sup> This may occur when folate stores become depleted in patients receiving therapeutic doses of aspirin.<sup>148</sup>

## EXCRETION

Thiamin deficiency can occur in patients treated with chronic loop diuretic therapy. Seligmann and colleagues reported that patients with

congestive heart failure treated with long-term furosemide therapy had increased urinary excretion of thiamin, leading to frank deficiency over time that may have contributed to poor cardiac performance.<sup>149</sup> Similar findings were reported by Brady and colleagues, who observed laboratory evidence of thiamin deficiency in congestive heart failure patients being treated with loop diuretics on a chronic basis.<sup>150</sup>

## DRUG-INDUCED FLUID AND ELECTROLYTE IMBALANCE

Several widely used medications can affect electrolyte balance, as summarized in Table 3. Sodium balance is altered by thiazide diuretics and the neuroleptic carbamazepine.<sup>151,152</sup> Patients treated long-term with carbamazepine have been reported to develop the syndrome of inappropriate antidiuretic hormone, resulting in hyponatremia and water retention.<sup>152</sup> In those patients, hyponatremia develops owing to the enhanced renal conservation of water. Similarly, patients receiving excessive diuretic therapy with fluid loss replaced with excessive water are prone to developing syndrome of inappropriate antidiuretic hormone.<sup>151</sup> Conversely, certain medications can cause hypernatremia as a result of water loss and subsequent dehydration. Hypernatremia, secondary to excessive lactulose therapy for hepatic encephalopathy or constipation, is a common drug-induced cause of this disorder.<sup>153</sup>

Renal wasting of potassium, resulting in hypokalemia, has been associated with thiazide and loop diuretics, corticosteroids, amphotericin B, and antipseudomonal penicillins.<sup>35</sup> Insulin and inhaled  $\beta_2$ -agonists (eg, albuterol) can cause a shift of potassium from the extracellular to the intracellular spaces.

Potassium-sparing diuretics (eg, spironolactone), angiotensin-converting enzyme inhibitors (eg, enalapril), heparin, and trimethoprim can cause hyperkalemia.<sup>154</sup> A variety of mechanisms are involved. Trimethoprim has weak diuretic properties with potassium-sparing activity.<sup>155</sup> Heparin can suppress aldosterone, leading to sodium wasting and potassium retention. Patients with renal insufficiency or diabetes mellitus appear to be more susceptible to heparin-induced hyperkalemia.<sup>156</sup>

The impact of medications on phosphorus balance is important in patients receiving nutritional support as the synthesis of new cells increases the need for phosphorus. Patients already at risk for refeeding syndrome are particularly susceptible to the effects of drugs known to decrease available phosphorus stores.<sup>157</sup> Drugs such as antacids and sulcralfate can alter the absorption of phosphorus from the GI tract by binding to dietary phosphate, thus preventing its absorption. Conversely, patients with renal dysfunction are at risk for development of hyperphosphatemia owing to the inherent phosphate content present in the phospholipid emulsifiers in intravenous fat emulsion or clindamycin phosphate injection.<sup>157</sup>

As previously discussed, medications such as isoniazid and cimetidine can inhibit the hepatic and/or renal hydroxylation of vitamin D, leading to impaired calcium absorption.<sup>158</sup> Odes and colleagues concluded that even short-term therapy with cimetidine altered vitamin D metabolism in humans.<sup>158</sup> The researchers came to this conclusion after studying 25-hydroxyvitamin D<sub>3</sub> levels for 30 days in patients treated with cimetidine.

Chronic corticosteroid use can cause a net negative calcium balance and increased bone resorption owing to suppressed intestinal absorption of calcium in conjunction with increased renal calcium and phosphate excretion and a subsequent decrease in renal tubular calcium resorption, resulting in bone osteopenia.<sup>119,159</sup> Even frequent use of inhaled steroids has been associated with this response.<sup>160</sup>

Hypomagnesemia as a result of renal wasting can occur in patients treated with loop diuretics, thiazide diuretics, amphotericin B, aminoglycosides, cisplatin, or cyclosporine. Cisplatin-induced hypomagnesemia is dose and duration dependent.<sup>161</sup> Cisplatin induces hypomagnesemia by reducing magnesium reabsorption in the ascending loop of Henle and the distal tubule.<sup>162</sup> Forastiere and colleagues reported that the total exposure of free platinum contributes to direct injury and renal toxicity.<sup>163</sup> Carboplatin, an antineoplastic with a chemical structure similar to cisplatin, has been reported to have a lower incidence of hypomagnesemia.<sup>164</sup>

Renal wasting of magnesium is also common in patients on prolonged courses of high doses of aminoglycosides.<sup>119,165</sup> Aminoglycosides can inhibit the proximal tubular transport of magnesium in the kidney, predisposing patients with already low intakes of magnesium to hypomagnesemia.<sup>165</sup>

If left untreated, hypomagnesemia will ultimately lead to hypocalcemia. Magnesium deficiency can induce a transient hypoparathyroidism by reducing the secretion of parathyroid hormone (PTH) and a blunted PTH response. This results in an inhibition of the hypocalcemic feedback loop.<sup>161</sup> Other agents, such as aluminum salts, also suppress PTH secretion, resulting in hypocalcemia. Treatment for hypocalcemia induced by hypomagnesemia involves correcting the hypomagnesemia first and then managing the magnesium losses. In some cases, calcium supplementation may be unnecessary.<sup>161</sup>

## TRACE ELEMENTS

Zinc is essential for the function of hundreds of enzymes such as dehydrogenases, aldolases, and peptidases and is involved in a variety of metabolic processes.<sup>166</sup> The formation and activation of zinc-dependent enzymes are regulated by zinc tissue levels.<sup>167</sup> Zinc metalloenzymes are responsible for structural integrity at the cellular level and for the regulation of various aspects of RNA and DNA metabolism.<sup>167</sup> Zinc deficiency limits the activity of these enzymes, resulting in decreased cell replication and tissue growth and repair.

Table 3 Examples of Drug–Nutrient Interactions

Medication/Drug Class	Nutrient	Interaction
Albuterol	Glucose	Hyperglycemia (in diabetics)
Aminoglycosides	Potassium, magnesium, sodium, calcium	Increased urinary excretion of potassium and magnesium, may also deplete sodium and calcium
Amphotericin	Magnesium, potassium, sodium	Electrolyte wasting
Aspirin	Folic acid	Decreased serum folate levels
Calcium carbonate	Iron	Decreased iron absorption
Captopril	Potassium	May cause hyperkalemia
Chloramphenicol	Protein, riboflavin B <sub>6</sub> , B <sub>12</sub>	Decreased protein synthesis
Cholestyramine	Fat, MCT, vitamins A, D, E, K, B <sub>12</sub> , folate, calcium, glucose, xylose	Decreased absorption
Cimetidine	Vitamin B <sub>12</sub>	Depletion of B <sub>12</sub> stores
Cisplatin	Magnesium	Magnesium depletion
Corticosteroids	Glucose	Hyperglycemia
Digoxin	Bran, fiber, calcium, magnesium, potassium	Decrease drug absorption; arrhythmias hypomagnesemia or hypokalemia may enhance toxic effect of digoxin; arrhythmias
Ethambutol	Copper, zinc	Copper and zinc depletion
Fluconazole	Potassium	Hypokalemia
Fluorouracil	Thiamine	Inhibits conversion of thiamine to thiamine pyrophosphatase; increase thiamine requirements
Foscarnet	Calcium, magnesium, phosphorus, potassium	Electrolyte wasting
Furazolidine	Tyramine-rich foods	Increased risk of hypertensive effects if used chronically or at high doses with tyramine-rich foods
Furosemide	Calcium, magnesium, potassium, sodium	Electrolyte depletion
Gemfibrozil	Vitamin E, ubiquinone	Decreased absorption
Insulin	Dextrose	Increased insulin requirements
H-2 antagonists (cimetidine, ranitidine, famotidine)	Vitamin B <sub>12</sub> , Zinc	Depletion of B <sub>12</sub> stores. May deplete zinc
Isoniazid	Pyridoxine, tyrosine-rich foods, histamine-rich foods, tyramine-rich foods	Vitamin B <sub>6</sub> antagonism blocks conversion of tyrosine to niacin. May cause headaches, itching, redness, chills, hypotension. Isoniazid has some MAO-I activity, tyramine-rich foods may cause hypertensive crisis
Linezolid	Tyramine-rich foods	Linezolid has some MAO-I properties, tyramine rich foods may cause hypertensive crisis
Lithium	Sodium	Increased sodium intake decreases lithium's effectiveness; decreased sodium intake may increase lithium toxicity
Methotrexate	Folic acid	Methotrexate may cause folate deficiency; folate supplementation may decrease methotrexate effects
Mineral oil	Fat soluble vitamins	Decreased absorption of fat soluble vitamins with chronic use
Neomycin	Fat soluble vitamins, MCT, B <sub>12</sub> , sodium, glucose, lactose, sucrose, xylose	Impaired absorption
Nonsteroidal anti-inflammatory agents	Potassium	Hyperkalemia in patients with renal disease or receiving potassium supplements or potassium sparing diuretics
Orlistat	Vitamin E	Reduced vitamin E absorption
Oral contraceptives	Ascorbic acid, folic acid, pyridoxine	Ascorbic acid, folic acid, and vitamin B <sub>6</sub> requirements increased
<i>para</i> -Aminosalicylic acid (PAS)	B <sub>12</sub> , folate, calcium, iron, magnesium	Decreased absorption of B <sub>12</sub> , folate, calcium, iron, magnesium
Penicillamine	Acidic foods/beverages	Decreased penicillamine absorption/inactivation
Penicillin	Acidic foods/beverages	Penicillin inactivation
Phenobarbital	Ascorbic acid vitamin D	Decreased ascorbic acid absorption Interferes with vitamin D metabolism
Phenytoin	Folic acid pyridoxine vitamin D	High-dose folic acid may antagonize phenytoin effects; phenytoin may cause folate deficiency resulting in megaloblastic anemia May antagonize phenytoin Interferes with vitamin D metabolism
Primidone	Folic acid	May cause folic acid deficiency leading to megaloblastic anemia
Proton pump inhibitors	Iron B <sub>12</sub>	Decreased absorption
Pyrimethamine	Folic acid	Decreased serum folate levels
Spirolactone	Sodium, potassium	May cause hyponatremia May cause hyperkalemia
Sulfasalazine	Folic acid	Inhibits the absorption of folic acid
Terbutaline	Glucose	Hyperglycemia (in diabetics)
Theophylline	Caffeine, carbohydrates, charcoal-broiled meat protein	Increases theophylline side effects. Decreased carbohydrate intake may decrease plasma half-life of theophylline. May decrease theophylline half-life. Increased protein intake may decrease plasma half-life of theophylline
Thiazide diuretics	Magnesium, potassium, sodium	Increased electrolyte wasting
Triamterene	Folic acid	May cause folic acid depletion
Trimethoprim	Folic acid	May cause folic acid depletion
Valproic acid	Carnitine	May cause carnitine deficiency with hyperammonemia
Warfarin	Vitamin K, onions, garlic, vitamin E	May inhibit warfarin response; increase dose needed. Excessive amounts may increase the fibrinolytic activity of warfarin. May enhance anticoagulant effect of warfarin
Zidovudine	Carnitine, folic acid	May cause carnitine deficiency. May cause megaloblastic anemia
Zonisamide	Biotin, vitamin B <sub>1</sub> , vitamin B <sub>2</sub> , niacin, pyridoxine, vitamin B <sub>12</sub> , vitamin K	May deplete stores.

**Table 4 Medications That Alter Glucose Metabolism/Response**

Medication/Drug Class	Response
Acritretin	Hyperglycemia
Amprenavir	Hyperglycemia
Arginine	Hyperglycemia
Corticosteroids	Hyperglycemia
Cyproheptadine	Hyperglycemia
Diazoxide	Hyperglycemia
Diuretics	Hyperglycemia
Epinephrine	Hyperglycemia
Fosphenytoin	Hypoglycemia
Glucagon	Hyperglycemia
Glycerol	Hyperglycemia
Indinavir	Hyperglycemia
L-asparaginase	Hyperglycemia
Megestrol	Hyperglycemia
Nelfinavir	Hyperglycemia
Nicotinic acid	Hyperglycemia
Oral contraceptives	Hyperglycemia
Octreotide	Hyper/hypoglycemia
Penicillamine	Hypoglycemia
Pentamidine	Hyper/hypoglycemia
Phenytoin	Hyperglycemia
Quinine	Hypoglycemia
Ritonavir	Hyperglycemia
Saquinavir	Hyperglycemia
Sertraline	Hyperglycemia
Tacrolimus	Hyperglycemia

Zinc interacts with several other nutrients. At supplemental doses, zinc may impair copper absorption.<sup>168</sup> Zinc deficiency can also negatively impact vitamin A metabolism by impairing the mobilization of retinol from the liver and altering retinal visual pigment metabolism, which may contribute to the night blindness seen in zinc deficiency.<sup>169</sup> It is thought that zinc deficiency may result in abnormal dark adaptation and/or age-related macular degeneration.<sup>170</sup>

Patients receiving PN are at risk for developing zinc deficiency. Zinc balance during PN depends on the infusion of zinc in amounts sufficient to offset urinary and GI losses that occur independent of zinc intake.<sup>171</sup> Premature infants receiving PN will experience a progressive decline in plasma zinc levels despite 14 days of continuous treatment, reflecting their high metabolic demands.<sup>171</sup>

## GLUCOSE

Patients with diabetes mellitus or others with insulin resistance (eg, severe infections, catabolic stress) are susceptible to the effects of medications known to impact glucose metabolism. Thiazide diuretics, corticosteroids, and cyclosporine have all been associated with inducing hyperglycemia in susceptible patients.<sup>172</sup> Hyperglycemia occurs in approximately 20% of patients treated with pentamidine.<sup>173</sup> Moreover, protease inhibitors have been recognized as a cause of hyperglycemia.<sup>174</sup> The long-acting somatostatin analog octreotide has been shown to inhibit insulin secretion and may result in a transient deterioration in

glucose tolerance on initiation of therapy.<sup>175</sup> In most cases, alteration of carbohydrate metabolism does not appear to be a problem. Table 4 lists some of the more common medications that alter glucose metabolism or response.

Hypoglycemia is the most common metabolic abnormality associated with pentamidine therapy.<sup>176</sup> The mechanism responsible for this adverse effect may involve a direct cytolytic effect on pancreatic beta cells, resulting in insulin release and hypoglycemia and a subsequent insulin deficiency owing to loss of beta cell function.<sup>177</sup> Eventually, however, pentamidine-induced pancreatic beta cell damage may lead to insulin deficiency and result in hyperglycemia, although this is considerably less frequent than hypoglycemia.<sup>177</sup>

Drugs or foods that have the ability to induce a rapid release of insulin can increase the risk of hypoglycemia, especially if taken with alcohol. Beta-blockers such as propranolol can inhibit glycogenolysis and, during periods of vigorous exercise, induce hypoglycemia.<sup>178</sup>

## FAT

With increased awareness of lipid abnormalities and coronary artery disease, drug-induced lipoprotein abnormalities must be considered; espe-

cially in patients in whom no other causes of dyslipidemia exist. Some of the most common causes of secondary dyslipidemia are medications. When a drug is used for a short period only, practitioners need to be aware of the effects on the patient's lipoprotein profile versus the chance that an underlying dyslipidemia has been exacerbated. Drugs used chronically may be more problematic as they may predispose the patient to atherosclerosis.<sup>179</sup> Table 5 lists medications associated with dyslipidemia.

Protease inhibitors interfere with some proteins involved in fat metabolism (ie, cytoplasmic retinoic acid-binding protein type 1).<sup>180</sup> Protease-inhibitor binding to low-density lipoprotein (LDL) receptor-related proteins (LRPs) impair hepatic chylomicron uptake and triglyceride clearance by the endothelial LRP-lipoprotein lipase complex. The resulting hyperlipidemia contributes to central fat deposition and insulin resistance.<sup>180</sup> It is also thought that protease inhibitors may also disrupt steroid hormone production, leading to lipodystrophy.<sup>181</sup> See Chapter 49, "Pediatric HIV Infection" for a full discussion of HIV lipodystrophy.

L-Asparaginase has been reported to cause abnormalities in lipid metabolism, ranging from hypocholesterolemia and hypotriglyceridemia to hypercholesterolemia and hypertriglyceridemia. Parsons and colleagues suggested that this alteration in lipid metabolism is caused by structural

**Table 5 Medications Associated with Dyslipidemia**

Medication	Total Lipids	Total Cholesterol	Triglycerides	Low-Density Lipoprotein	High-Density Lipoprotein	Very Low Density Lipoprotein
Abacavir			↑			
Amiodarone		↑	↑			
Amprenavir		↑	↑			
Anabolic steroids				↑	↓	
Beta-blockers			↑			
Calcitriol		↑				
Cholestyramine			↑			
Cyclosporine	↑	↑	↑	↑		
Dexrazoxane			↑			
Didanosine			↑			
Disopyramide		↑	↑			
Efavirenz		↑	↑		↑	
Enoxaparin	↑					
Ergocalciferol		↑				
Estrogen			↑			
Fluconazole		↑	↑			
Glucocorticoids	↑	↑	↑	↑	↓	↑
Interferons			↑			↑
Isotretinoin		↑	↑		↑	
Itraconazole			↑			
L-asparaginase			↑			
Miconazole (IV)	↑	↑				
Mycophenolate		↑				
Nelfinavir	↑					
Paclitaxel			↑			
Phenothiazines						
Progestins			~	↑	↓	↓
Propofol	↑					
Retinoids (vitamin A)			↑	↑	↓	↑
Risperidone			↑			
Ritonavir		↑	↑			
Sertraline		↑	↑	↑		Possible ↑
Tacrolimus				↑		↑
Valproic acid						↑

changes in the high-density lipoprotein (HDL) particles from higher to lower density that is reflected in an altered ratio of lipid to protein.<sup>182</sup> The authors suggested that prior to the initiation of L-asparaginase therapy, HDL-cholesterol particles are protein rich but gradually become lipid rich because of an asparaginase-associated reduction in protein synthesis. They also concluded that modifications in asparaginase therapy are not necessary; however, close monitoring is recommended for patients whose triglyceride levels exceed 2,000 mg/dL when the risk of pancreatitis is increased.

In addition to asparaginase-associated lipid abnormalities, patients being treated for acute lymphoblastic leukemia often receive corticosteroids that may alter lipid and lipoprotein metabolism by increasing hepatic cholesterol synthesis.<sup>182</sup> Corticosteroids increase the frequency of hypercholesterolemia and hypertriglyceridemia with elevations in LDL and HDL levels, often in a dose-related manner.<sup>179</sup> Females appear to be more susceptible than males to these changes. Switching to alternate-day therapy may reduce lipoprotein levels in some patients.<sup>179</sup>

Orally administered estrogens decrease serum LDL and increase serum HDL levels in a dose-related manner.<sup>179</sup> Moreover, these agents are known to increase serum triglyceride levels by 30 to 87%.<sup>179</sup> It has been suggested that low-dose estrogens be used to minimize elevations in triglyceride levels without compromising their favorable impact on LDL and HDL levels.<sup>179</sup> Interestingly, other routes of estrogen administration (topical, intradermal, intramuscular) tend not to have as pronounced an effect on lipoproteins, perhaps because these routes bypass first-pass metabolism through the liver, thus having a smaller impact on hepatic protein synthesis.<sup>179,183</sup>

Progestins, often used in combination with estrogens in various oral contraceptive products, can also affect lipoprotein levels. Generally, progestins elevate LDL levels and decrease triglyceride, HDL, and very low density lipoprotein levels, correlating with the androgenic activity associated with specific progestins.<sup>179</sup> Newer low-dose triphasic oral contraceptives (eg, ethinyl estradiol-levonorgestrel, ethinyl estradiol-norethindrone) do not have any appreciable alterations in lipid profiles or at best mild increases in serum cholesterol, LDL, and triglycerides.<sup>183</sup>

Like estrogens, anabolic steroids can also cause profound, dose-related effects on lipoprotein metabolism. Reductions in HDL levels in conjunction with an elevation in LDL levels are often seen in patients using these agents.<sup>179</sup> The exact mechanism has not yet been defined, but caution is advised in using these agents in patients prone to dyslipidemia or atherosclerosis.

## GASTROINTESTINAL ADVERSE EFFECTS

Many medications can adversely affect the function of the GI tract. Most are minor and resolved over time without any specific intervention.

Others, however, can be significant and resulting in severe GI illness (eg, esophagitis, colitis) that can negatively impact the tolerance to an oral or tube fed diet. Drug induced esophagitis can occur with doxycycline capsules, iron sulfate tablets, extended release potassium chloride tablets, and tetracycline.<sup>184</sup> Typically, this occurs in adolescents who drink inadequate amounts of fluid with their medications, or patients with left atrial enlargement or cardiomegaly as the heart impinges on the esophagus, thus increasing the transit time of the medication in the esophagus. Switching to a liquid medication or administering the problematic drug with plenty of water often helps alleviate the situation.

## DRUGS AND APPETITE

Impairment of nutritional status owing to drug use often results in drug-induced nutritional deficiencies in those cases in which the medication results in appetite suppression and decreased food intake. Often these signs and symptoms of nutrient deficiencies are nonspecific and may mimic those of other diseases and conditions.

Drugs can reduce food intake through a variety of mechanisms. Drugs that affect appetite (Table 6) may do so by either a central or peripheral effect, including loss of appetite, inducing sedation, or evoking adverse response when food is ingested.<sup>185</sup> The primary effect typically centers around appetite suppression, a centrally acting mechanism that includes the catecholaminergic (eg, dextroamphetamine), dopaminergic (eg, levodopa), serotonergic (eg, fenfluramine), and

endorphin (eg, naloxone) modulators, which may all act to suppress appetite.<sup>186</sup> Peripherally acting mechanisms that can indirectly suppress appetite include those agents that inhibit gastric emptying (eg, levodopa) or bulking agents (eg, methylcellulose).

A secondary response may also occur when an adverse response to food caused by the drug results in a loss of appetite. The emetic center, located within the brainstem, is easily stimulated by the action of many drugs. These include drugs that cause nausea and vomiting (eg, digoxintoxic dose), drugs causing a loss of taste (eg, penicillamine), drugs causing stomatitis (eg, fluorouracil), and hepatotoxic agents (eg, alcohol).<sup>185</sup>

Another way in which medications can cause anorexia is through depletion of various nutrients. High-doses of aluminum- or magnesium-containing antacids can result in phosphate depletion, leading to muscle weakness and anorexia.<sup>187</sup> Similarly, loop diuretics can lead to depletion of sodium, potassium, and magnesium, which can result in anorexia.<sup>188</sup> Drugs known to deplete folate, such as phenytoin, sulfasalazine, and trimethoprim, can result in weight loss and anorexia.<sup>189</sup> Penicillamine, which induces zinc depletion, can lead to diminished taste acuity and possibly decreased food intake.<sup>190</sup> Ironically, even a nutrient can induce anorexia. Belle and Halpern reported that patients taking relatively large doses of niacin for hyperlipidemia experienced GI symptoms that resulted in poor appetite and moderate weight loss.<sup>191</sup>

Zinc supplements have been used to treat drug-induced hypogeusia with mixed results. Although zinc supplementation has been used successfully to manage hypogeusia in patients undergoing dialysis, Dahl and colleagues did not see similar findings when patients with acetazolamide-induced taste disturbances were given zinc supplements.<sup>192</sup>

In some cases, weight gain may be an undesirable side effect of a medication. Antiepileptic drugs, both old and new, have weight changes associated with their use. Antiepileptic drugs associated with marked weight gain include carbamazepine, gabapentin, VPA and vigabatrin. Lamotrigine and levetiracetam are both considered weight-neutral, whereas felbamate and topiramate have been associated with significant weight loss.<sup>193</sup>

## APPETITE ENHANCERS

Appetite enhancers are useful in reversing the anorexia of disease, in particular cancer cachexia and HIV wasting. Several medications are frequently used, although none have yet become a standard of therapy.

The appetite-boosting properties of corticosteroids have been well established.<sup>194</sup> Their impact on weight gain seems to be short term, however. Moertel and colleagues suggested that patients treated with dexamethasone saw appetite improvement after 2 weeks of treatment, but the

**Table 6 Drugs That Affect Appetite**

Drugs That Decrease Appetite	Drugs That Stimulate Appetite
Aluminum hydroxide	Benzodiazepines
Amphetamines	Clemastine
Cisplatin	Cyproheptadine HCl
Cholestyramine	Dronabinol
Dactinomycin	Glucocorticoids
Digoxin	Insulin
Ethambutol	Lithium
Furosemide	Megestrol acetate
Griseofulvin	Oral contraceptives
Hydralazine	Phenothiazines
Hydroxychloroquine	Tricyclic antidepressants
Hydroxyurea	
Itraconazole	
Lamivudine	
Methenamine	
Methotrexate	
Methylcellulose	
Mineral oil	
Nitrofurantoin	
Penicillamine	
Sibutramine	
Spirolactone	
Sulfasalazine	
Thiazide diuretics	
Topiramate	

Adapted from reference 67.

effect disappeared by week 4.<sup>195</sup> Some attribute the improved appetite to the mood-enhancing properties of steroids rather than a specific effect on appetite.<sup>196</sup> The antihistamine cyproheptadine has become one of the most commonly used appetite stimulants in pediatric patients, particularly those with anorexia nervosa. It is a potent serotonin antagonist. By decreasing brain serotonin levels, appetite is enhanced and food intake is increased, resulting in weight gain.<sup>197</sup> Megestrol acetate is a drug with antiestrogen properties whose original indication was in the treatment of breast cancer. It was one of the first drugs used to treat HIV wasting. It is a powerful appetite stimulant, and weight gain seen with its use is substantial, although it tends to be mostly fat, with minimal increases in lean body mass.<sup>198</sup> Megestrol also lowers testosterone levels in males, which may explain its minimal increases in lean body mass. Adrenal suppression has also been reported with long-term megestrol use; thus, abrupt discontinuation should be avoided.<sup>199</sup> Megestrol acetate also has been used to stimulate appetite and promote weight gain in a limited number of patients with cachexia associated with neoplastic disease. Although the exact mechanism of action has not been determined, it has been suggested that megestrol and/or its metabolites may, either directly or indirectly, stimulate appetite, resulting in weight gain, or may alter metabolic pathways by interfering with the production or response of mediators such as cachectin, a hormone that inhibits adipocyte lipogenic enzymes.<sup>200</sup>

Dronabinol is a derivative of marijuana that is primarily used in pediatric patients as an antiemetic but has some use in treating anorexia, primarily in HIV wasting.<sup>201</sup> Like megestrol, it can stimulate appetite as well as interest in food. Its effects on mental status, however, limit its usefulness.

Because cytokine effects on appetite can contribute to the anorexia of disease, anticytokine monoclonal antibodies and receptor antagonists may have a role in inhibiting cytokine action.<sup>202</sup> Some agents, such as the corticosteroids, inhibit the transcription of interleukin-1, tumor necrosis factor, and other cytokines. Other agents appear to act by binding a mitogen-activating protein kinase necessary for the translation of messenger RNAs.<sup>202</sup> Fish oil supplements that are rich in omega-3 fatty acids decrease the anorectic effect of interleukin-1 and tumor necrosis factor.<sup>203</sup> Unfortunately, the fishy taste associated with these supplements makes them a less than desirable option.

## APPETITE SUPPRESSANTS

Although, for long-term success, weight loss takes a great deal of self-control to resist the many internal and external cues to eat, appetite suppressants can augment weight loss by reducing the hunger drive, thereby assisting the patient to adhere to a restricted caloric diet.<sup>204</sup> The major class of drugs currently in use for the adjunctive treatment is the centrally acting appetite

suppressants. This class is further subdivided into those that act on the noradrenergic nervous system and those that act on the serotonergic nervous system.

Given their high potential for abuse and numerous side effects, the noradrenergic agents (eg, dextroamphetamine) are no longer routinely used in weight loss management unless other therapies have been proven ineffective. These agents block the reuptake of dopamine and norepinephrine from the synapse, thus increasing the amount available in the cerebral cortex and reticular activating system.<sup>204</sup>

The neurotransmitter serotonin is responsible for appetite suppression and satiation. Serotonin, as part of a complex negative feedback loop, accumulates in certain areas of the brain in response to feeding.<sup>204</sup> Fenfluramine, dexfenfluramine, and fluoxetine inhibit serotonin reuptake at presynaptic spaces. They have few central stimulatory effects.

Other agents that have the potential to cause anorexia and may have a potential role in weight loss management are the thermogenic drugs.<sup>205</sup> These include endogenous hormones (ie, insulin, thyroid hormone) and sympathomimetic agents with alpha- or beta-adrenergic properties.<sup>205</sup> Currently, exogenous thyroid has no role in obesity management owing to its adverse effects on protein breakdown, cardiovascular complications, and bone mineralization.<sup>206</sup>

## VITAMIN AND MINERAL SUPPLEMENTATION/HPERVITAMINOSIS

Megavitamin therapy has been advocated in the treatment of various disease states, including schizophrenia, cancer, and the common cold.<sup>207</sup>

A megadose is generally considered to be 10 or more times the recommended dietary allowance.<sup>208</sup> Although excess water-soluble vitamins are excreted and usually cause few problems, side effects have been reported in cases of excessively high doses.<sup>209</sup> Dietary supplementation can also impact response to medications. If used carelessly, vitamin and mineral supplementation alone or as part of a fad diet can potentiate or exacerbate nutrient–nutrient interactions, as summarized in Tables 7 and 8.

Drug-metabolizing enzyme systems have been shown to be highly dependent on vitamin C status. Houston and colleagues showed that normal individuals receiving supplemental ascorbic acid had a substantial increase in antipyrine clearance, whereas Beatie and Sherlock reported that vitamin C deficiency was partly responsible for impaired drug clearance in patients with liver disease.<sup>210</sup> When ascorbic acid is taken in excessive amounts, enzyme saturation occurs, and the vitamin acts as a chemical and enters into nonenzymatic reactions.<sup>211</sup> Ascorbic acid is a strong reducing agent and is able to impact other dietary components as well as alter drug disposition.<sup>211</sup> Ironically, scurvy, the main deficiency state associated with inadequate dietary intake of ascorbic acid, a relatively rare condition today, can occur in infants born to mothers taking large doses of vitamin C.<sup>211</sup> Both the mother and fetus increase their metabolic destruction of ascorbic acid after maternal ingestion of large doses of ascorbic acid. At birth, any dietary ascorbic acid ingested by the infant is degraded rapidly, leading to a deficiency state. Reports of acute scurvy have been reported in infants breast-fed by mothers who had ingested more than 400 mg vitamin C daily during pregnancy.<sup>212</sup> A similar situation can occur in adults

**Table 7 Examples of Nutrient–Nutrient Interactions**

Nutrient	Interaction
Calcium	High calcium intake interferes with manganese, phosphorus, and iron absorption. Calcium absorption is potentiated by vitamin D, reduced by dietary oxalates. Excessive protein intake may increase calcium losses
Chromium	A high-sugar diet may increase urinary chromium losses
Copper	High intake may impair zinc absorption
Cysteine	May chelate with copper in parenteral nutrition solutions
Iron	Iron salts might decrease gastrointestinal zinc resorption; impairs manganese absorption Soy products, including soy-based infant formula, significantly reduce absorption of iron vitamin C enhances absorption of iron Calcium salts may reduce iron absorption vitamin A deficiency increases liver storage of iron
Magnesium	High magnesium intake may impair calcium absorption, decreases phosphorus absorption
Manganese	Calcium and iron salts decrease manganese absorption zinc enhances manganese absorption
Phosphorus	High intake decreases magnesium absorption
Thiamine	High carbohydrate diet or intravenous dextrose may increase thiamine requirement
Zinc	High zinc intake may impair copper absorption. Zinc may increase manganese absorption Iron salts may impair zinc absorption
Vitamin A	Megadoses may interfere with iron, iodine, copper, calcium absorption; can also interfere with absorption of ascorbic acid, vitamin K, vitamin E, and vitamin D
Vitamin C	Increases iron absorption, impairs copper absorption, interferes with cyanocobalamin absorption
Vitamin D	Reduced intake impairs calcium and phosphorus absorption and utilization
Vitamin E	Inhibits the reticulocyte and hemoglobin response to iron

**Table 8 Examples of Vitamin–Drug Interactions**

Nutrient	Medication	Interaction
Ascorbic acid (vitamin C)	Coumarin anticoagulants, gentamicin, iron salts, oral contraceptives, tricyclic antidepressants	Shortens prothrombin time, may antagonize warfarin response; acidifies urine, decreases efficacy of gentamicin; increased iron absorption; intermittent use may cause contraceptive failure; megadoses (>2 g/d) may reduce therapeutic response of tricyclic antidepressants
Folic acid	Phenytoin, pyrimethamine	Reduces phenytoin bioavailability, may antagonize anticonvulsant action of phenytoin; reduces pyrimethamine efficacy
Niacin	Adrenergic blockers, aspirin, HMG-CoA reductase inhibitors (“statins”), isoniazid	Enhances vasodilation, may cause orthostatic hypotension aspirin decreases flushing seen with niacin use; increased risk of statin-associated myopathy/rhabdomyolysis with concurrent use; increased niacin requirement seen with isoniazid use
Pyridoxine (vitamin B <sub>6</sub> )	Barbiturates, levodopa, phenytoin	Reduced barbiturate response, reduces levodopa response; megadoses may impair phenytoin effect, cause decrease in phenytoin levels
Vitamin A	Aluminum hydroxide, coumarin anticoagulants, isotretinoin, oral contraceptives	Reduced vitamin A absorption; megadoses of vitamin A can enhance anticoagulant response, increase risk of bleeding; isotretinoin competes with vitamin A; increases serum vitamin A levels
Vitamin D	Digoxin	Vitamin D may cause hypercalcemia, leading to arrhythmias
Vitamin E	Coumarin anticoagulants, vitamin A, iron salts	Potentiates anticoagulant response; increases serum vitamin A levels; inhibits the reticulocyte and hemoglobin response to iron therapy
Vitamin K	Coumarin anticoagulants	Antagonizes anticoagulant response

Adapted from reference 67.

dependent on large doses of vitamin C. Therefore, it is recommended that patients receiving megadoses of vitamin C not be abruptly stopped but rather tapered by 10 to 20% until discontinued or on maintenance doses. Other complications associated with megadoses of ascorbic acid include vitamin B<sub>12</sub> deficiency. Herbert and Jacob reported that even ascorbic doses as little as 250 mg may destroy up to 81% of cyanocobalamin in a moderate vitamin B<sub>12</sub>-containing meal and up to 25% in a vitamin B<sub>12</sub>-rich meal.<sup>213</sup> To blunt the intensity of this interaction, the authors suggested that ascorbic acid be taken two or more hours after meals. Oxalate stones may occur in susceptible patients receiving doses of greater than 4 g/d of ascorbic acid. Auer and colleagues reported that a hematuria and calcium oxalate dihydrate crystal formation in a 25-year-old male 8 days after ingesting 4 g of ascorbic acid daily resolved 5 days after discontinuing ascorbic acid supplementation.<sup>214</sup>

The daily consumption of vitamin B<sub>6</sub> (pyridoxine) in doses of 50 to 500 mg is not unusual given the currently available strengths of over-the-counter products. High-doses, however, may have a toxic action on the nervous system.<sup>215</sup> Sensory neuropathies have been reported in adults who received daily doses of 2 g of pyridoxine over a 4-month period or as soon as 2 months when daily doses of 5 g were ingested.

Megadoses of folic acid given to patients on long-term phenytoin therapy exhibit seizures and electroencephalogram abnormalities.<sup>216</sup> It appears

that folic acid supplementation increases phenytoin liver metabolism; studies suggest increased phenytoin parahydroxylation and another suggests increased O-methylation of the catechol metabolite.<sup>217</sup> Another study concluded that folic acid does not stimulate phenytoin metabolism, but rather it changes the rates of elimination.<sup>218</sup>

Trace elements such as manganese can also impact the absorption of other nutrients such as iron. In patients with iron deficiency, there is a greater absorption of manganese. When iron supplementation occurs, there is a corresponding decrease in the amount of manganese absorbed with a greater amount appearing in the feces. This interaction appears to be due to competition for similar binding and absorption sites of (nonheme) iron and manganese.<sup>219</sup>

Hypervitaminosis A and D has been described in children, but the occurrence is rare.<sup>220,221</sup> Both are life threatening on an acute basis; vitamin A may cause increased intracranial pressure, whereas vitamin D may cause fatal hypercalcemia. Infants and young children are especially susceptible to excessive doses of vitamin A. Acute toxicity has been reported in infants receiving doses of 50,000 to 100,000 µg (166,666 to 333,333 IU) retinol as palmitate. Individual variation is significant, however. Field studies have used periodic massive doses of vitamin A, with thousands of 1- to 6-year-old children receiving 200,000 IU of retinyl palmitate (60,000 µg retinol), with approximately 1% exhibiting signs of

intolerance that disappeared within hours of administration.<sup>222</sup> Chronic toxicity seen in infants and young children usually results from daily doses of 10,000 to 50,000 µg (33,333 to 166,666 IU) for several months.<sup>223</sup> Symptoms gradually disappear on discontinuation. The American Academy of Pediatrics recommends that daily vitamin A supplementation of more than 3,000 µg (10,000 IU) for young children be used under medical supervision.<sup>224</sup>

In typical doses, vitamin D is used to prevent and treat rickets.<sup>225</sup> Serious poisoning can occur with excessive doses. Sustained daily intake of as little as 1,800 IU in children has been reported as toxic.<sup>226</sup> Excessive vitamin D leads to increased absorption of calcium from the GI tract and enhanced bone resorption, with a subsequent loss of renal concentrating ability. Children typically will present with anorexia, vomiting, polyuria, or irritability associated with the increased serum calcium concentrations.<sup>227</sup> It should be noted, however, that very high doses of vitamin D have been effective in some patients with hereditary vitamin D-resistant rickets.<sup>228</sup> Hereditary vitamin D-resistant ricket accompanied by alopecia reflects a more severe form of vitamin D receptor resistance and is rarely responsive to vitamin D. Initial ergocalciferol therapy for children with vitamin D-resistant rickets is 1,000 to 2,000 µg/d (40,000 to 80,000 U) with phosphate supplement. The daily dose is increased at 3- to 4-month intervals in 250 to 500 µg (10,000 to 20,000 U) increments.<sup>229</sup>

In 1992, an outbreak of hypercalcemia owing to vitamin D intoxication was noted. In the case series, eight patients suffered vitamin D toxicity that was traced to excessive amounts of the vitamin in milk produced by a single dairy.<sup>230</sup> These were the first reported cases of hypervitaminosis D from commercial food products in the United States since fortification became commonplace in the 1930s. A second study summarized the findings of an analysis of 42 containers of milk and 10 cans of infant formulas from supermarkets in five states.<sup>231</sup> Nearly two-thirds of the milk container samples had less than 80% of the stated amount, whereas 4 of the 42 samples had over 120% of the labeled vitamin D content. The 10 infant formulas tested had vitamin D levels ranging from 111 IU/100 kcal to 250 IU/100 kcal, exceeding the maximum permitted by the US Food and Drug Administration regulation of 100 IU/100 kcal. Food and Drug Administration-compliant studies on both dairy products and infant formulas compiled over a 10-year period also showed some variance in vitamin D levels but not to the extent that would constitute a health risk.<sup>232</sup>

Vitamin K-rich foods (ie, green leafy vegetables, cabbage, broccoli), when intake is irregular, can alter response to anticoagulants such as warfarin. When ingested in high amounts, these foods can be associated with anticoagulant failure, resulting in the need for higher doses. Similarly, when patients who have been stable on warfarin suddenly decrease their intake of these vitamin K-rich foods, they can put themselves at risk for bleeding because they are suddenly receiving too

large a warfarin dose. Warfarin creates a partial deficiency of the active form of vitamin K involved in the post-translational modification factors (II, VII, IX, X, and proteins C and S).<sup>233</sup> Other sources of vitamin K, such as intravenous fat emulsions that are prepared from soybean or safflower and soybean oils, contain phytosterols that contain vitamin K.<sup>234</sup> Warfarin resistance has been reported in patients taking warfarin who also received intravenous fat emulsions.<sup>234</sup> This interaction presumably occurs because of the vitamin K content of the intravenous fat emulsion. Frequent monitoring of the international normalized ratio and warfarin dosage adjustments are imperative in these patients.

## CONCLUSION

The human diet is highly heterogeneous in its composition, method of preparation, quantity, and time of consumption. Consequently, drug kinetics as a result of diet varies widely in subjects based on age, gender, culture, and economic status. Even within the same individual, seasonal variations will occur that impact dietary habits and ultimately drug-related effects. Although each factor may play a small role by itself, a much larger synergistic effect could occur when combined with other dietary factors, as well as genetic and environmental factors.

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