Phosphate Additives in Food: You Are What You Eat—But Shouldn't You Know That?

By Sharon M. Moe

Phosphorus levels are elevated in patients with chronic kidney disease due to decreased urinary excretion. Higher levels of blood phosphorus are associated with increased mortality in patients on dialysis, patients with kidney disease not yet on dialysis, and in the general population. In animal studies, adding phosphorus to the diet causes calcification of arteries and progression of kidney disease.

In the petri dish in the lab, adding phosphorus to artery vascular smooth muscle cells results in a change of the cell to become a bone-like cell and to calcify. This and other data support the hypothesis that phosphorus is a true uremic toxin and a risk factor for adverse health in the more than 20 million individuals with kidney disease in the United States. Unfortunately, data from the National Health and Nutrition Examination Survey (NHANES) and other studies demonstrate that nearly all Americans eat food that contains far more phosphate than either the estimated average requirement or the recommended dietary allowance.

The approach to kidney patients with elevated phosphorus levels includes the use of phosphate-binding compounds, increased dialysis time, and diet adjustment. It is the latter that becomes tricky. It requires a savvy consumer to truly follow a low-phosphorus diet. Phosphorus is in all proteins, and thus any protein source will be high in phosphate (dairy, meat, or legumes/beans). However, in legumes/beans, the phosphate is bound to phytate. Humans lack the ability to digest phytate as they do not have the enzyme phytase (in contrast to most farm animals). Thus, there is decreased bioavailability, or intestinal absorption, of plant-based sources of phosphate. Short-term studies have demonstrated that vegetarian diets can reduce phosphorus levels and the hormonal elevations in parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23) that result from increased phosphorus absorption. Whether such diets are efficacious and safe long term in kidney patients has not been studied.

A major source of phosphorus in the diet is not from the diet itself, but rather additives that contain inorganic phosphate salts. These additives will be nearly 100 percent bioavailable, meaning they are completely absorbed across the intestine. They are commonly used in canned and boxed food processing to improve taste, texture, color, and cooking time, and act as a preservative. They are also added to meat and poultry products to help retain moisture and protect flavor. Unfortunately, there is an increasing use of these additives by food manufacturers.

Foods that contain additives have nearly 70 percent higher phosphate content than similar foods without additives. These additives are listed on the U.S. Food and Drug Administration's GRAS (Generally Recognized As Safe) list and specific quantitation on the food label is voluntary (and rarely listed). In contrast, these additives must be listed in the ingredients but these diverse chemical names can be confusing to patients, especially those with low health literacy. One study instructed patients to use a magnifying glass to look at foods and avoid the ones that included ingredients with the letters "Phosphor." The result was a reduction in phosphorus levels in these patients. This should be a call to action to label food as "contains phosphate additives" so that patients and consumers alike know what they are eating. An alternative would be to ban the additives completely.

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Foods and Nutrients That Interact with Medications by Altering the Function of Metabolism and/or Transport Pathways

By Melanie S. Joy

Clinicians are trained to review prescription drugs with patients during their clinic visits and hospital admissions. However, less emphasis is placed on appropriate review and documentation of foods and nutrients that are known or suspected to interact with medications. This scenario places kidney disease patients at significant risk, given the 10 to 12 different medications that are typically prescribed (1). Although the clinician's time is a limiting factor in conducting nutrient reviews, an even greater problem is the lack of knowledge by clinicians of what nutrients can interact with which drugs and the mechanisms for the interactions. The purpose of this article is to inform clinicians caring for patients with kidney disease by providing a concise overview of nutrients—defined as vitamins, minerals, herbs, and food supplements—that can interact with prescribed medications.

When patients purchase prescription medications from a retail or mail-order pharmacy, either they are counseled by a pharmacist or they receive medication information handouts that address drug–drug interactions. However, patients who purchase over-the-counter nutrients are not counseled by a professional with training about the interactions between nutrients and medications. Further complicating the clinical scenario is the lack of dose standardization between the various over-the-counter nutrient products. Patients are also unaware of the safety issues related to nutrients, such as co-contamination with drugs or toxins. Recent reports suggest that approximately one-third of patients who are prescribed medications consume over-the-counter nutrients, demonstrating the need to understand and screen for potential drug–nutrient interactions (2).

The common understanding of nutrient interactions with drugs is usually limited to warfarin, whereby patients are counseled about the need to maintain the same daily amount of green leafy vegetables in their diet to limit fluctuations in the international normalized ratio. This fairly well-known interaction is secondary to increases in the amount of vitamin K substrate available for blood clotting. The interaction between warfarin and green leafy vegetables is well known to clinicians, and this information is usually forwarded to patients taking warfarin.

Beyond warfarin, clinicians have limited knowledge regarding drug–nutrient interactions and the mechanisms of these interactions. Although several mechanisms can account for drug–nutrient interactions, the remainder of this article will focus on the interactions known to occur with the drug disposition pathways of metabolism and transport.

The liver and kidney are the primary organs for drug metabolism. Mechanistically, nutrients can alter the function of drug-metabolizing enzymes and transporters (3–9). Nutrients can cause induction or inhibition of metabolizing enzymes, leading to reduced or increased activity, respectively, of victim drugs. Common drug metabolizing enzymes are cytochrome P450s, glutathione S-transferases, and uridine diphosphate glucuronosyltransferases. Transporters move drugs across membranes and are commonly found in the liver, kidney, and intestine. Common drug transporters are P-glycoprotein and organic anion transporting polypeptides. Induction and inhibition of transporters by nutrients can occur. However, the effect on transport of the victim drug is dependent on whether uptake or efflux transporters are affected. For uptake transporters, induction would increase and inhibition would decrease intracellular drug exposures. For efflux transporters, induction would decrease and inhibition would increase drug intracellular exposures. Intestinal absorption is a special transport case whereby enhanced efflux from inside the enterocyte interior and back to the intestinal lumen leads to decreased absorption.

Metabolism and transport pathways often work in concert, whereby increased transport uptake function and decreased efflux function would enable the enhanced presence of drug available to intracellular metabolizing enzymes. Some examples of induction and inhibition of drug metabolism and transport pathways

by nutrients are provided in Table 1 (3–9). Although the table primarily includes interactions that have been specifically assessed, the reader is cautioned that extensive studies documenting all the victim drugs that could be affected by each nutrient have not been conducted.

Drug–nutrient interactions in patients with kidney diseases require extensive study secondary to the number of medications prescribed to these patients. Evolving literature also suggests changes to drug metabolism and transport function secondary to kidney diseases per se (10, 11). The triad of polypharmacy, altered function of drug disposition pathways, and ingestion of over-the-counter nutrients with potential for drug interaction predisposes patients with kidney disease to adverse reactions and outcomes. More emphasis on screening and education of kidney disease patients regarding potential drug–nutrient interactions is needed.

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Table 1. Drug–nutrient interactions

Pathway	Effects	Herb/Nutrient	Common Victim Drugs
CYP3A4, UGTs, P-glycoprotein	Induction	Hyperforin: St. John's wort	Cyclosporine, tacrolimus, digoxin, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, etoposide, paclitaxel, vinblastine, vincristine, vindesine
CYP3A4, CYP2D6	Inhibition (MB)	Berberine, hydrastine: goldenseal	Midazolam (CYP3A4 probe), cyclosporine, amitriptyline, clozapine, codeine, desipramine, donepezil, flecainide, fluoxetine, meperidine, methadone, tramadol
CYP3A4	Inhibition	Furanocoumarins: grapefruit juice, Seville orange juice	Benzodiazepines (triazolam, midazolam, diazepam, alprazolam), ritonavir, sertraline, cyclosporine, buspirone, levothyroxine, oxycodone
CYP2E1	Inhibition	Allyl sulfides, isothiocyanates: garlic, watercress	Acetaminophen, chlorzoxazone
CYP1A2, CYP2E1	Inhibition	Sulfur-containing glucosinolates: cruciferous vegetables	Acetaminophen, chlorzoxazone, haloperidol, theophylline
GSTs, UGTs	Induction	Cruciferous vegetables	Acetaminophen
CYP2C19	Induction	Ginkgo biloba	Omeprazole
CYP2C9, CYP2C19, CYP3A4, OATPs	Inhibition	Silymarins: milk thistle	Losartan, omeprazole, midazolam, warfarin, simvastatin, felodipine, rosuvastatin, nifedipine
CYP3A4, CYP2C9	Inhibition	Ginseng	Warfarin
CYP3A4	Inhibition	Echinacea	Midazolam, estrone 3-sulfate
CYP3A4, CYP2D6, P-glycoprotein, UGTs	Inhibition	Piperaceae: black pepper	Phenytoin, rifampicin, propranolol, theophylline, nevirapine
GSTs, CYP3A4 P-glycoprotein	Induction Inhibition	Ginger	Midazolam, digoxin
CYP3A4, P-glycoprotein	Induction	Vitamin D	Midazolam, digoxin
CYP3A4, CYP1A2	Inhibition	Resveratrol	Cisapride, cyclosporine, testosterone

Abbreviations: CYP = cytochrome P450; GSTs = glutathione S-transferases; OATPs = organic anion transporting polypeptides; UGTs = uridine diphosphate glucuronosyltransferases.