Use of Dietary Supplements in Living Kidney Donors: A Critical Review

Amanda K. Leonberg-Yoo, David Johnson, Nicole Persun, Jehan Bahrainwala, Peter P. Reese, Ali Naji, and Jennifer Trofe-Clark

Dietary supplement use is high among US adults, with the intention by users to promote overall health and wellness. Kidney donors, who are selected based on their overall good health and wellness, can have high utilization rates of dietary supplements. We provide a framework for the evaluation of living kidney donors and use of dietary supplements. In this review, dietary supplements will include any orally administered dietary or complementary nutritional products, but excluding micronutrients (vitamins and minerals), food, and cannabis. Use of dietary supplements can influence metabolic parameters that mask future risk for chronic illness such as diabetes and hypertension. Dietary supplements can also alter bleeding risk, anesthesia and analgesic efficacy, and safety in a perioperative period. Finally, postdonation monitoring of kidney function and risk for supplement-related nephrotoxicity should be part of a kidney donor educational process. For practitioners evaluating a potential kidney donor, we provide a list of the most commonly used herbal supplements and the effects on evaluation in a predonation, perioperative donation, and postoperative donation phase. Finally, we provide recommendations for best practices for integration into a comprehensive care plan for kidney donors during all stages of evaluation. We recommend avoidance of dietary supplements in a kidney donor population, although there is a paucity of data that identifies true harm. Rather, associations, known mechanisms of action, and common sense suggest that we avoid use in this population.

Introduction

Use of complementary and alternative medicine is expanding in the United States, with dietary supplement use now reported from >50% of US adults and with sales accounting for >$14 billion.1,2 The most common self-reported reasons for use of dietary supplements are to improve or maintain overall health.3 This is relevant among a population of living kidney donors, who are selected based on a baseline healthy lifestyle, which in many cases may include perceived health benefits from dietary supplements. Many individuals may be unfamiliar with the differences in regulatory standards between drugs approved by the US Food and Drug Administration (FDA) and dietary supplements and thus assume that these supplements are safe for consumption.

Though the prevalence and risks of dietary supplement use have been previously discussed in transplant recipients, with reported use between 35% and 38%, little is known about the effects of dietary supplements in a kidney donor population.1,4-6 A single-center retrospective review of 157 living kidney donors who donated in our large academic transplantation center between September 30, 2016, and September 30, 2018, found 24% reporting dietary supplement use at the first evaluation, with 41% of the living kidney donors taking more than 1 supplement preoperatively. The most commonly reported dietary supplement at both visits was omega-3 fatty acids, glucosamine/chondroitin, and probiotics.7

The primary purpose of this review is to discuss the clinical evaluation of a kidney donor using dietary supplements in the evaluation (preoperative), perioperative, and postoperative phases. The secondary purpose is to provide a practical tool for clinicians to use in a kidney donor evaluation process to minimize unrecognized and unnecessary harms related to dietary supplement use. Careful evaluation of dietary supplement use and the period in which potential kidney donors use them is critical to the safe care of this group of patients.

Dietary Supplements and Regulatory Standards

Dietary supplements are part of a larger approach termed complementary and alternative medicine, which refers to a nonmainstream approach that is either combined with conventional medicine (complementary) or takes the place of mainstream medicine (alternative). Dietary supplements are defined by the Dietary Supplement Health and Education Act as a product containing 1 or more specified dietary ingredients (vitamin, mineral, herb or botanical [other than tobacco], or amino acid) that is intended to supplement the diet. At the time of this writing, cannabis is excluded from this definition because a dietary supplement cannot contain any active ingredients in an FDA-approved drug or authorized for investigation as a new drug. Dietary supplements are orally ingested and do not include other topical or homeopathic products.5 Differences in premarketing notifications, proof of efficacy and safety, postapproval surveillance, and disease treatment claims represent the major divergences in regulatory standards between FDA-approved medications and dietary supplements (Table 1).9 In this review, dietary supplements will include any orally administered dietary or complementary nutritional products, but excluding micronutrients (vitamins and minerals) and foods.
Table 1. Regulatory Standards for FDA-Approved Medications and Dietary Supplements

<table>
<thead>
<tr>
<th>Regulatory Standard</th>
<th>FDA-Approved Medications</th>
<th>Dietary Supplements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Premarket notification</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Proof of efficacy</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Proof of safety</td>
<td>Required</td>
<td>Not required</td>
</tr>
<tr>
<td>Postapproval surveillance</td>
<td>Required</td>
<td>Required (as of 2007)</td>
</tr>
<tr>
<td>Current Good Manufacturing Practice</td>
<td>Required</td>
<td>Required (as of 2007)</td>
</tr>
<tr>
<td>Disease treatment claims</td>
<td>Allowed via approval</td>
<td>Not allowed</td>
</tr>
</tbody>
</table>

Abbreviation: FDA, US Food and Drug Administration.

Although there has been evidence about the efficacy of certain dietary supplements, data from these studies are very poor and there has been little consideration for possible side effects and supplement-drug interactions. Dietary supplements are not subject to the same manufacturing regulatory standards as approved medications and therefore can be at risk for an unknown contaminant that could potentially cause nephrotoxicity. The FDA has published dietary supplement Current Good Manufacturing Practices, which require dietary supplement companies to use proper controls to ensure that products are manufactured and processed in a consistent manner. However, there is no requirement for companies to submit FDA quality control testing data for their products. In attempts to promote safety, the US Pharmacopoeia has provided standards for the quality, purity, and safety of dietary supplements, although not all dietary supplement manufacturers follow these quality standards.

Predonation Considerations

Opportunities to enhance access to kidney transplantation have become a major focus for treatment options for kidney failure, with emphasis on living donation. In a recent national public opinion survey, 73% of people indicated that they would be willing to donate a kidney. Assessment of a living donor involves a comprehensive general medical evaluation, psychosocial risk assessment, and a multidisciplinary review of the individual’s candidacy. This multidisciplinary transplantation team includes nephrologists, surgeons, psychiatrists, social workers, nurse coordinators, physician assistants, nurse practitioners, an independent living donor advocate, pharmacists, dieticians, and financial coordinators. Key factors during the preoperative evaluation of a kidney donor candidate are baseline health and risk for future chronic comorbid conditions, including kidney disease. These future risk assessments can be challenging if a medication or dietary supplement influences the metabolic evaluation, including assessment of diabetes mellitus, cardiovascular disease, or kidney function, to name a few. In the same single-center retrospective review that identified 24% reported use of dietary supplements in a donor population, only 13% reported dietary supplement use at the first point in evaluation, whereas an additional 24 potential donors identified use of a dietary supplement at a later point in their evaluation, often very close to the surgical date (mean time between preoperative visit and donation was 9 ± 5 [standard deviation] days). This emphasizes the need to review dietary supplement use at each clinic visit and with both nephrologists and pharmacists.

Dietary supplement use can influence the assessment of diabetes mellitus during preoperative testing, which is generally assessed by fasting glucose measurement, hemoglobin A1c (HbA1c) level, or a measure of glycemic response to an oral glucose load. For example, individuals taking supplemental doses of cinnamon may have subtle improvements in glycemic control, which can influence interpretation of future diabetes risk. In a randomized controlled trial of 58 patients with diabetes mellitus type 2, ingestion of cinnamon, 2 g, orally daily for 12 days showed a significant reduction in HbA1c levels compared to placebo (mean baseline and day 12 HbA1c values of 8.22% and 7.86% vs 8.55% and 8.68%, respectively). In this small study, the degree of diabetes control among each of the study arms and short-term exposure to the intervention may have influenced the positive results. A meta-analysis of 5 randomized controlled trials evaluating cinnamon supplementation in individuals with type 1 or type 2 diabetes mellitus failed to show significant changes in HbA1c or fasting blood glucose levels compared with placebo. In nondiabetic individuals, an observed reduction in postprandial glucose response was noted, although 2-hour postprandial glucose response was similar in those exposed to dietary cinnamon compared with those without cinnamon supplementation. Despite the poor quality of evidence, cinnamon may influence the interpretation of common metrics for diabetes mellitus, thus masking a potential abnormal glucose level in a donor population. We suggest avoidance during an evaluation for living donor kidney candidacy.

Cardiovascular risk profile in a donor population is assessed by parameters including a lipid profile and blood pressure assessment, both of which can be influenced by the use of certain dietary supplements (Table 2). Several studies of animals and humans have evaluated the role of curcumin, a polyphenol from turmeric, and have shown positive health benefits, including modulation of vascular smooth muscle cell proliferation and improvement in fasting lipid panels. In a meta-analysis of randomized controlled trials, use of turmeric and curcumin significantly reduced serum low-density lipoprotein cholesterol and triglyceride levels, although serum high-density lipoprotein cholesterol levels were not statistically different in comparison to a control group. Biases in this meta-analysis include nonuniform use of curcumin and/or

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Table 2. List of Dietary Supplements

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Phase</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aloe</td>
<td>Preoperative</td>
<td>Blood glucose: 136 obese pre- or early diabetic patients given aloe, 147 mg/d, vs placebo and showed decreased insulin resistance at 4 wk and fasting blood glucose at 8 wk</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Kidney function: Prolonged use at dose &gt; 1 g/d implicated in acute nephrotoxicity</td>
</tr>
<tr>
<td>Ashwagandha</td>
<td>Preoperative</td>
<td>Blood glucose: Decreased in patients with schizophrenia who took a total of 1,200 mg/d vs those on placebo</td>
</tr>
<tr>
<td></td>
<td>Perioperative</td>
<td>Sedation: There is historical use for this substance in Ayurvedic medicine, but no data</td>
</tr>
<tr>
<td>Bioflavonoid</td>
<td>Preoperative</td>
<td>BP: Various doses of different flavonoids have been shown to decrease SBP and/or DBP; the decrease in BP was not consistent</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Drug-drug interactions: Shown to be significant inhibitors of Pgp</td>
</tr>
<tr>
<td>Black cohosh</td>
<td>Preoperative</td>
<td>BP: In vitro vasodilation in rats has been shown</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Drug-drug interactions: These extracts have been shown to be mild to potent inhibitors of a number of CYP enzymes</td>
</tr>
<tr>
<td>Cherry fruit</td>
<td>Preoperative</td>
<td>BP: 20 women and 17 men aged 65-80 y randomly assigned to 480 mL of tart cherry juice for 12 wk or a control drink; treatment group had a larger reduction in SBP than control ( (P = 0.04) )</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Kidney function: 82-y-old man, admitted for elevated Scr (3.3 mg/dL) and hyperkalemia ( (K, 6 \text{ mEq/L}) ) had been taking 2-4 oz of cherry concentrate daily for 1 mo to gout prevention; 1 mo after discontinuation, Scr and potassium were 1.7 mg/dL and 4.4 mEq/L, respectively</td>
</tr>
<tr>
<td>Cinnamon</td>
<td>Preoperative</td>
<td>Blood glucose: In 58 patients with T2DM, 2 g of cinnamon daily for 12 d significantly reduced HbA1c</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>BP: In 58 patients with T2DM, 2 g of cinnamon daily for 12 d significantly reduced SBP and DBP</td>
</tr>
<tr>
<td>Cranberry</td>
<td>Preoperative</td>
<td>Kidney damage: Case report of daily ingestion of cranberry tablets for 6 mo leading to severe flank pain and hematuria with the presence of oxalate stones</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Drug-drug interaction: Interaction with warfarin</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Postdonation</td>
<td>Drug-drug interaction: Human pharmacokinetic studies have shown the inhibition of metabolism by CYP1A2, 2C9, 2D6, 3A4</td>
</tr>
<tr>
<td>Fennel</td>
<td>Postdonation</td>
<td>Drug-drug interaction: 5-methoxypsoralen identified as a major component and constituent of fennel that inhibits CYP3A4</td>
</tr>
<tr>
<td>Fenugreek</td>
<td>Preoperative</td>
<td>Blood glucose: In randomized controlled parallel study in prediabetics, fenugreek, 10 g/d, given for 3 y was associated with lower conversion to diabetes than controls</td>
</tr>
<tr>
<td></td>
<td>Perioperative</td>
<td>Bleeding: Aqueous extracts of fenugreek found to inhibit coagulation process in vitro and significantly prolonged prothrombin time</td>
</tr>
<tr>
<td>Flax seed</td>
<td>Preoperative</td>
<td>BP: Flax meal contains SDG, which has a potent hypotensive effect in rats given 10-mg/kg dose with peak effect at 20 min and duration up to 4 h postdose</td>
</tr>
<tr>
<td></td>
<td>Perioperative</td>
<td>Bleeding: Flaxseed oil decreased platelet aggregation in healthy man who received 40 g/d for 23 d; flaxseed oil has also been associated with increased bleeding</td>
</tr>
<tr>
<td>Garlic</td>
<td>Perioperative</td>
<td>Bleeding: Inhibition of platelet function (based on case report of patient consuming garlic, 12 g, daily with concomitant SSRI before cervicothoracic spine decompression)</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Drug-drug interaction: In vitro studies show increased secretion by Pgp and other drug transporters and &lt;50% inhibition of CYP1A2, 2B6, 2C9, 2C19, 2D6, and 3A, but only modest or unlikely inhibition of CYP3A4</td>
</tr>
<tr>
<td>Ginger</td>
<td>Preoperative</td>
<td>Blood glucose: Reduction in fasting blood glucose (based on randomized, double-blind, placebo-controlled trial of 88 T2DM patients receiving 3 g of ginger powder capsules daily for 8 wk)</td>
</tr>
<tr>
<td></td>
<td>Perioperative</td>
<td>Bleeding: 5 of 20 constituents of ginger have been shown to have antiplatelet effect in vitro; case reports have shown elevated INR and epistaxis related to ginger</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Perioperative</td>
<td>Bleeding: Case series of spontaneous bleeding events with dose ranging from 75-600 mg/d for 1 wk to 2 y in duration</td>
</tr>
<tr>
<td></td>
<td>Postdonation</td>
<td>Drug-drug interactions: Though not shown in vivo to result in drug-drug interaction, doses of ginkgo &gt; 360 mg/d shown to have a weak induction effect on CYP2C19 and weak inhibitory effect on CYP3A4</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Preoperative</td>
<td>Blood glucose: Doses of 3 g/d of ginseng root shown to significantly reduce 2-h postprandial glucose in T2DM</td>
</tr>
<tr>
<td>Green tea</td>
<td>Preoperative</td>
<td>BP: Meta-analysis of 11 studies in 821 people who were healthy or at high risk for CVD: mean difference in SBP (-3.18 \ (95% \ CI, (-5.25 ; to ; -1.11) ) mm Hg; DBP, (-3.42 \ (95% \ CI, (4.54 ; to ; -2.30) )</td>
</tr>
<tr>
<td></td>
<td>Perioperative</td>
<td>Bleeding: Active ingredient EGCG inhibits platelet aggregation and also decreases binding of fibrinogen to platelet surface GPIIb/IIIa</td>
</tr>
</tbody>
</table>

(Continued)
turmeric formulation and heterogeneity between the trials regarding baseline health features.

Another example is cherry fruit, which when consumed as a concentrate has been shown to reduce systolic blood pressure in a randomized controlled trial involving 34 people. Although not statistically significant, the group treated with cherry concentrate had a reduction in systolic blood pressure by 4.1 mm Hg, whereas a control group showed an increase in systolic blood pressure by 5.4 mm Hg after a 12-week intervention. Arguably, assessment of these risks is replicated with additional evaluation in a potential donor (ie, cardiovascular evaluation on imaging.
and repeat blood pressures), and the quality of evidence surrounding true changes in metabolic health parameters is not strong. These studies have a risk for publication bias and are of low-quality evidence. However, there may be subtle changes in perceived cardiovascular risk that may attenuate certain cardiovascular and metabolic risk parameters.

Candidate donors undergo careful assessment of glomerular filtration rate (GFR), as well as markers for kidney damage (ie, proteinuria and microscopic hematuria), with the goal to most accurately determine true kidney function and ensure no long-term risk for kidney dysfunction in the future. Assessment of GFR is often performed using the creatinine-based CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) estimating equation. Additional methods for assessment of GFR include creatinine clearance, cystatin-based estimated GFR, or measured GFR using exogenous clearance markers. The use of dietary supplements may affect the assessment of GFR by alteration of exogenous creatinine generation. In a controlled single-patient study, a 20-year-old man who had undergone a unilateral nephrectomy received 20 g of creatine monohydrate supplementation per day. GFR was monitored using serum creatinine level and $^{51}$Cr-EDTA clearance measurement. Although a change in serum creatinine level was observed (from 1.03 mg/dL before creatine supplementation to 1.27 mg/dL after), there was no difference in $^{51}$Cr-EDTA clearance measurement (81.6 pre- vs 82.0 mL/min/1.73 m$^2$ postexposure). Thus, a short course of creatine supplementation in a patient with a solitary kidney did not compromise GFR; however, the ability to accurately estimate it was affected. Masking of proteinuria, as a marker for kidney damage, can also occur in individuals who ingest turmeric as a dietary supplement. In individuals with known kidney disease (lupus nephritis), turmeric was shown to significantly decrease proteinuria compared with baseline over 3 months ($260.9 \pm 106.2$ vs $954.2 \pm 836.6$ mg/dL).

An association between the use of dietary supplements and incidence of nephrolithiasis has also been well described. The decision to consider potential donors with prior episodes or incidental findings of nephrolithiasis is dependent on the assessment of stone recurrence risk and the potential risk for obstructive nephropathy in a unilateral kidney following donation. There are no consensus guidelines regarding the selection of individuals with kidney stones, although the most up to date KDIGO (Kidney Disease: Improving Global Outcomes) guideline (from 2017) suggests that individuals with prior or current kidney stones be evaluated using metabolic evaluation (ie, serum chemistries, parathyroid hormone, and 24-hour urine collection for urine chemistries including total volume, pH, calcium, oxalate, uric acid, citrate sodium, potassium, and creatinine).

The use of cranberry as a preventive measure for urinary tract infections is of particular concern in kidney donors given the risk for stone formation from cranberry supplements due to increased urinary oxalate concentrations. Donor candidates at minimal risk for nephrolithiasis recurrence taking concomitant cranberry supplements pose a particularly vexing clinical situation. These individuals require a broader discussion about the timing of re-evaluation for kidney stone recurrence following dietary supplement cessation, as well as assessment of biochemical risk factors to uncover any underlying metabolic risk that may have been influenced by dietary supplement use.

**Perioperative Risk**

Although there are no specific data related to dietary supplementation causing harm during donor nephrectomy surgery, bleeding complications may be influenced by the use of dietary supplements. Due to unpredictable pharmacokinetics and inconsistent manufacturing practices, discontinuing supplements that could affect hemostasis or sedation should be considered as soon as possible. The American Society of Anesthesiology recommends that dietary supplements be discontinued 1 to 2 weeks before surgery out of maximal precaution, although this recommendation is rarely followed. In a survey study investigating the use of dietary supplements in patients undergoing surgery, 16.5% and 19% of patients were taking a dietary supplement with a potential drug interaction with sedation or coagulation, respectively. Of the surgical patient taking dietary supplements with the potential to affect coagulation, 12.5% had an actual intraoperative hemorrhage.

Bleeding complications attributable to dietary supplements may have several mechanisms, including alteration in platelet activation and interaction with components of the coagulation cascade (Table 2). Dietary supplements that inhibit platelet aggregation include flaxseed oil and green tea supplements containing the active ingredient epigallocatechin-3 gallate. Omega-3 fatty acids (commonly known as fish oil), which have been used for cardiovascular effects, have been shown in vitro to cause inhibition of platelet-to-platelet adhesion and platelet-stimulated thrombin generation. However, in a large placebo-controlled trial randomized to receipt of perioperative fish oil versus placebo, there was no increase in perioperative bleeding in the treatment arm. Dietary supplements associated with alteration in coagulation cascade include turmeric and its active ingredient curcumin, and fenugreek, an herb native to the Mediterranean region. These dietary supplements have been shown to prolong activated partial thromboplastin time (curcumin) and prothrombin time (curcumin and fenugreek). The active ingredients in ginger supplements, frequently used to manage nausea, have been shown to exhibit antiplatelet effects in vitro, as well as increase international normalized ratio with concomitant use of warfarin. Conflicting data on the risk for bleeding exist with saw palmetto, garlic, and ginkgo. However, case reports of
bleeding with these supplements have also been described. Although not all are clearly defined causal relationships, the potential risk for bleeding complications for an elective surgery should be minimized by discontinuation of potential agents.

Surgical risk for myositis or rhabdomyolysis, rare among the donor population, may be amplified with medication or dietary supplement use. In general, laparoscopic surgery is preferred for kidney donation due to improved healing time, reduction in surgical mortality, and shorter hospital stays. In both laparoscopic donor nephrectomy and microinvasive open surgical nephrectomy, positioning of the patient to achieve visualization results in prolonged torsion and limb flexion. In laparoscopic radical nephrectomy for nondonor reasons, there has been a case report of acute kidney injury due to rhabdomyolysis. Risk factors for this include prolonged surgical time, poor optimization of volume status, thermal extremes, or other medications that can predispose to myositis. Red yeast rice and its active 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor component lovastatin are known causes of drug-induced rhabdomyolysis. Although red yeast rice products with this component have been banned by the FDA from sale as dietary supplements since 1998, the FDA has reported that as recently as 2011, red yeast rice products have been tested and shown to contain significant amounts of lovastatin. No product could be confirmed as passing Current Good Manufacturing Practices. Additionally, these products may contain significant amounts of nephrotoxins, including citrinin. It is clear that attempts at regulation of these products may not be as effective as expected. Additionally, though not identified as top purchased supplements in 2016, wormwood oil (Artemisia absinthium), licorice, creatine monohydrate, and the combination supplement Hydroxycut (Iovate Health Sciences) have been shown to indirectly influence rhabdomyolysis. Although most risk factors for myositis or rhabdomyolysis can only be modified by intraoperative management, we recommend perioperative cessation of dietary supplements associated with theoretical or known higher risk for myositis or rhabdomyolysis.

Certain dietary supplements have sedative properties independent of anesthesia, and more importantly, the dietary supplement–drug interaction can alter the safety profile of prescribed medications. Many medications used in anesthesia are metabolized by the cytochrome P-450 (CYP450) pathway, and pharmacokinetic contributions of dietary supplements may either attenuate or enhance the sedative properties of certain anesthetics. Examples of sedative agents (independent of pharmacokinetic influence) include ashwagandha and valerian root, with the latter potentially inhibiting γ-aminobutyric acid metabolism as well. Additionally, the holy basil species Ocimum sanctum has been shown to increase total diazepam-induced sleep time in a dose-dependent manner. Kava, also well known for its sedative effects, has been shown to potentiate γ-aminobutyric acid and the effects of barbiturates and benzodiazepines. The influence of dietary supplements on postoperative analgesia is necessary to consider in the postoperative period as well.

**Postdonation Considerations**

In a postdonation setting, there is heightened concern for potential nephrotoxicity given the presence of a unilateral kidney. In general, kidney donation is considered safe with no difference in long-term mortality between living donors and matched controls. There is 5- to 8-fold increased relative risk for kidney failure after donation, although the absolute risk for kidney failure remains small in donors with similar baseline demographics. In a US population, the estimated risk for kidney failure 15 years postdonation was 30.8 (95% confidence interval [CI], 24.3-38.5) per 10,000 kidney donors, as compared to 3.9 (95% CI, 0.8-8.9) per 10,000 among matched healthy non-donors. Although the absolute risk remains small, it is relevant from a monitoring perspective to mitigate any potential risk for future kidney function decline in a kidney donor population. Special attention for the potential of direct or indirect renal toxicity from drugs and dietary supplements in the post–kidney transplantation population is warranted. More specifically, several dietary supplements have been shown to affect blood pressure, fluid balance, or directly and indirectly cause nephrotoxicity.

The prevalence of hypertension post–kidney donation is similar to the average US population. In a single-center cohort from the University of Minnesota, approximately one-third of kidney donors develop hypertension postdonation. In this cohort, risk factors for developing hypertension were similar to a general population. The use of dietary supplements can influence changes in blood pressure. For example, daily consumption of licorice increased blood pressure by 7/4 [95% CI, 2-11/1-8] mm Hg. Additionally, a case report describes an elevation of blood pressure in a nonhypertensive patient to 145-160/95-110 mm Hg after self-medication with a St. John’s wort extract for 5 weeks. Blood pressure normalized within 2 days of discontinuation.

On the opposite spectrum, the unintended diuretic effect of dietary supplements can lead to hypotension. Horsetail, documented to be used by patients as an astringent, as well as other conditions, is frequently used by the American public and has been shown to be a potent diuretic. In a randomized double-blind trial, the use of horsetail extract (900 mg/d) had comparable diuretic effect (measured by water balance over a 24-hour period) as hydrochlorothiazide, 25 mg/d, in 36 healthy male volunteers. Postdonation, single-nephron GFR remains constant, although single-kidney GFR increases in the setting of parallel increases in renal plasma flow. Although these dietary supplements may not directly lead to nephrotoxicity, unintentional relative volume depletion by diuretic therapy or otherwise may have a
greater impact on reduction in GFR by reduction in renal plasma flow.

Nephrotoxic potential has been observed with exposure to several dietary supplements. Although at times the mechanism and causality can be unclear (whether it be related to adulterants vs direct nephrotoxicity), a variety of foods that are ingested have been associated with nephrotoxicity. Mechanism have included direct nephrotoxicity (aristolochic acid), alterations in renal blood flow (turmeric and kava), nephrolithiasis (ephedra), and rhabdomyolysis (creatine monohydrate), to name a few. Inhibition of cyclooxygenase and resultant altered renal hemodynamics have been described with use of kava.

Correlation between direct nephrotoxicity and dietary supplements has most clearly been associated with the development of tubulointerstitial disease following ingestion of supplements adulterated with aristolochic acid, the primary constituent of Aristolochia. In an initial case series, a Belgian weight loss clinic prescribing a weight-loss formula inadvertently substituted Aristolochia fangchi, a nephrotoxic herb, resulting in 2 cases of acute kidney injury with fibrosing interstitial nephritis. More than 100 cases were reported, and the incidence of kidney injury following receipt of the weight loss regimen was 3% to 5%.

In a unique situation of using creatine supplementation in a patient with a solitary kidney, the use of creatine did not alter kidney function; however, creatinine clearance measurements were incorrect, leading to a misclassification of acute kidney injury due to influences of creatine supplementation on creatinine clearance measurements.

**Conclusions**

Guidance on the use and role of dietary supplements in the kidney donor population is woefully absent. In this particular population, the highest level of caution should be prescribed to minimize any augmented risk to an individual donor. In practice, we discourage the use of dietary supplements, described in this article as an orally administered product intended to supplement the diet, excluding micronutrients, cannabis, and foods. We recommend discontinuing dietary supplements 1-2 wk or longer before donation.

**Box 1. Best Practices for Evaluation of Dietary Supplements in Living Kidney Donors**

**Predonation evaluation: First in-person visit with living donor team until donation date is scheduled**

- Include dietary supplement definition, use, and reporting standards in the donor education process
- Review all dietary supplements with transplant pharmacist and nephrologist during evaluation, separated from “medication use”
- Consider influence of dietary supplements on clinical parameters during evaluation phase using Table 2 as a guide
- Instruct donor candidates to avoid initiation of new dietary supplements
- Discuss preferred use of dietary supplements that are US Pharmacopeia verified or NSF certified
- Recommend discontinuing dietary supplements 1-2 wk or longer before donation

**Perioperative evaluation: Preoperative visit until time of hospital discharge**

- Re-review all dietary supplements with transplant pharmacist
- Review risk for bleeding complications with continuation of dietary supplements using Table 2
- Review dietary supplement–drug interactions related to anesthesia or postoperative analgesia
- Consider use of the Naranjo Adverse Drug Reaction Probability Scale if adverse outcomes occur perioperatively to assess dietary supplement involvement

**Postdonation management: After hospital discharge and onward**

- Recommend avoidance of routine use of dietary supplements after kidney donation
- If a kidney donor wishes to continue dietary supplements, discuss preferred use of products that are US Pharmacopeia verified or NSF certified
- Review nephrotoxic potential of dietary supplements using Table 2

Note: Dietary supplements defined here as a product (other than tobacco) intended to supplement the diet, excluding micronutrients, cannabis, and foods.
supplements, as well as those who are not; (2) incorporation of dietary supplement data use in living donors at the time of donation and postdonation as part of the United Network for Organ Sharing data collection; (3) development of multidisciplinary best practice guidelines through national and international living kidney donor–focused organizations, including live donor patient education materials and patient input; (4) subsequent assessment of outcomes once guidelines are put into practice; and (5) implementation of more stringent regulatory requirements for all dietary supplements.

The Kidney Care Initiative executive order aims to double the number of kidneys available to transplant by 2030 in part by increasing living donation rates through mitigating financial barriers to living donors.93 Hence, it is anticipated that transplantation centers over time will see an increase in evaluation of both living donors and potential recipients, with supplement use assessment and directions for management being an integral part of their evaluation. We suggest using the table of dietary supplements (Table 2) as a tool to assist providers in evaluating risk for harm or risk for modification with use of the supplement pre- and postoperatively. Given the vast supplement supply, knowledge of all dietary supplement risks and dietary supplement–drug interactions is not an expectation. We propose using this article as a “best practices” guide for evaluation of dietary supplement use in a potential kidney donor (Box 194). However, this should not surpass clinical judgment or the need for additional testing on a case-by-case basis.

Article Information

Authors’ Full Names and Academic Degrees: Amanda K. Leonberg-Yoo, MD, MS, David Johnson, PharmD, Nicole Persun, PharmD, Jehan Bahrainwala, MD, Peter P. Reese, MD, MSCE, Ali Naji, MD, PhD, and Jennifer Trofe-Clark, PharmD.

Affiliations: Renal-Electrolyte & Hypertension Division, Department of Medicine, Perelman School of Medicine, University of Pennsylvania (AKL-Y, JB, PPR, JT-C); Penn Medicine Transplant Institute (AKL-Y, DJ, JB, PPR, AN, JT-C), and Department of Pharmacy Services (DJ, NP, JT-C), Hospital of the University of Pennsylvania, Philadelphia, PA; Alexion Pharmaceuticals, Inc, Boston, MA (DJ); Department of Pharmacy, Allegheny Health Network, Pittsburgh, PA (NP); and Department of Biostatistics, Epidemiology and Informatics (PPR), and Transplantation Division, Department of Surgery (AN), Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA; Penn Medicine Transplant Institute, Pittsburgh, PA (NP); and Department of Pharmacy Services, Hospital of the University of Pennsylvania, Grounds Roads Bldg–Pharmacy Services, 3400 Spruce St, Philadelphia, PA 19104. Email: jennifer.trofe-clark@pennmedicine.upenn.edu

Address for Correspondence: Jennifer Trofe-Clark, PharmD, BCPS, Department of Pharmacy Services, Hospital of the University of Pennsylvania, Grounds Roads Bldg–Pharmacy Services, 3400 Spruce St, Philadelphia, PA 19104. E-mail: jennifer.trofe-clark@pennmedicine.upenn.edu

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References


