ADVANCES IN PRACTICE:
Dietary supplement use in patients with chronic kidney disease

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Dietary supplements are defined as products containing one or more of the following ingredients: a vitamin or mineral; an herb or other botanical; an amino acid; a dietary substance to supplement the diet by increasing total nutrition intake; or a concentrate, metabolite, constituent extract or combination of these ingredients (1). A dietary supplement is further defined as a product intended for ingestion in the form of a tablet, capsule, powder, softgel, gelcap or liquid form.

During the past three decades, dietary supplement use has increased by up to 29% among adults, and dietary supplements now rank third in over-the-counter product sales (2,3). Findings from an ancillary study to the 1995-1996 Washington State Cancer Risk Behavior Survey indicated that participants took dietary supplements to feel better and prevent chronic diseases (4).

Other studies reveal that patients with chronic diseases are the most frequent users of dietary supplements. A cross-sectional study of 45,748 U.S. adults aged 50 to 75 years showed that use of multivitamin supplements plus 16 individual vitamins and minerals was higher in participants whose medical history included cancer, cardiovascular disease and other self-reported medical conditions (5). Information on supplement use, health status and hospitalizations in 11,775 adults who participated in the 1986 National Health Interview Survey suggests that supplement use is more likely and more intense among individuals with one or more chronic health problems (6).

The issue of vitamin and mineral supplementation in patients with chronic kidney disease (CKD) is important for renal nutrition professionals. Absorption, retention and activity of vitamins and minerals in patients with CKD are impacted by nutrition restrictions, uremic toxins and drug-nutrient interactions (7). Patients with CKD Stage 5 undergoing maintenance dialysis therapy experience loss of water-soluble vitamins during dialysis at rates exceeding loss with normal urinary excretion (7). Vitamin and mineral bioavailability in elderly patients may be affected not only by declining renal function but also by low acidity in the stomach, which impairs absorption of folic acid, vitamin B-12, calcium, iron and beta-carotene (8). In maintenance dialysis patients, deficiencies have been reported most commonly for vitamin C, folic acid, vitamin B-6, 1,25-dihydoxycholecalciferol, iron, zinc and selenium (9).

According to the Renal Dietitianís Standards for Clinical Practice, renal dietitians are responsible for prescribing nutrition therapy based on analysis of biochemical parameters (10). More recently, in its proposal for revision of conditions of coverage for renal providers, Centers for Medicare and Medicaid Services (CMS) specified that the renal dietitian's responsibilities include monitoring vitamin and mineral supplementation in their patients (11). Of concern to all health care providers is the fact that despite widespread availability of dietary supplements in supermarkets, specialty stores and via the Internet, their distribution is not subject to standards applied to prescription and over-the-counter medications. Dietary supplements are regulated as foods, and there is no requirement for demonstration of effectiveness unless health claims are made in advertising or labeling (12). In this column, patterns of vitamin and mineral intake in patients with CKD will be reviewed and recommendations regarding vitamin and mineral supplementation for these patients will be summarized.

Patterns of dietary supplement use in patients with CKD

Information about a patient's current vitamin and mineral intake, as well as dietary supplement use, is needed to make recommendations and interventions regarding vitamin and mineral supplementation. Several recent studies have evaluated vitamin and mineral intake from food, and use of vitamin and mineral supplements in patients with CKD.

Block's food frequency questionnaire (version 98) was administered to 30 adult maintenance hemodialysis (MHD) patients (mean age 55.8±14.6 years) who were randomly selected from a pool of patients in a community dialysis unit (13). Vitamin and mineral intake was lower in MHD patients than in a control group without any known kidney

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disease. Statistically significant differences were observed between the MHD and control groups for vitamin C, and for the carotenoids cryptoxanthin and lycopene. Eleven MHD patients reported taking the renal multivitamin Nephrovite® (R&D Laboratories, Marina del Ray, CA) at least four times per week. Use of this multivitamin resulted in significantly higher vitamin B6 intake than in nonusers and control individuals.

In another study of vitamin and mineral intake in MHD patients, 25 patients (mean age 49.3±12.9 years) received standardized instruction on keeping food records and estimating portion size before completing 9-day food records (14). Findings from this investigation indicated a wide range of vitamin and mineral intake for the small study group. Mean daily calorie intake correlated strongly with intake of vitamin E, vitamin B2, calcium, phosphorus and potassium. Mean daily protein intake correlated most strongly with vitamin B6, niacin, iron and phosphorus intake. While most patients consumed 100% of the recommended dietary allowances (RDAs) for niacin and vitamin B12, mean daily intake of vitamins A and B6 were least likely to exceed two-thirds of the RDA.

Vitamin and mineral intake has also been compared with RDAs in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) (15). Seven-day food frequency questionnaires completed by 242 CAPD patients (mean age 55 ± 12 years) showed that intakes of iron, zinc, calcium, phosphorus and most water-soluble vitamins, except vitamin B12, were low in most patients. Vitamin C intake was below the RDA in almost 50% of patients and was particularly deficient in those with low residual renal function and total urea clearance. Also noted was a low intake of calories and B vitamins in patients with poor residual function and low urea clearances.

A cross-sectional survey of 100 adults (age >18 years) with CKD stages 2 through 5 used a detailed questionnaire to collect data on dietary supplements consumed, sources of information regarding dietary supplements and participants' perceptions of health improvement resulting from supplement use (16). Prevalence of dietary supplement use in this study group was 45% and number of dietary supplements used ranged from one to five or more daily. Most commonly used dietary supplements were vitamin E (50% of supplement users), multivitamin/mineral products (47%) and vitamin C (29%). Supplement use occurred most frequently in the early stages of CKD and decreased as renal failure progressed. Supplement users obtained information about dietary supplements from a variety of sources including physicians (27%), printed materials (27%), naturopaths/herbalists (20%), the Internet (13%), friends and family (6%) and allied health professionals (5%). Seventy-six percent of supplement users reported health improvements as a result of dietary supplement use. When compared with non-users, dietary supplement users were significantly more concerned with their health and preferred involvement in health-related decisions.

Collectively, these studies indicate wide variability in vitamin and mineral intake among patients with CKD. Patients undergoing maintenance dialysis therapy may be particularly at risk for low intake of vitamin B6 and vitamin C (13-15). However, variability in micronutrient intake among patients underscores the need for renal nutrition professionals to identify current vitamin and mineral intake to determine appropriate and individualized levels of supplementation for their patients. High incidence of vitamin E supplementation in patients with CKD may be of concern due to its ability to increase bleeding risk in patients who are also taking the anticoagulant warfarin (16,17).

Recommendations for vitamin and mineral supplementation in patients with CKD

Table 1 summarizes general guidelines for vitamin supplementation in patients with CKD. As more information about vitamin status and metabolism in CKD becomes available, these recommendations are likely to change (19). The pharmacological use of some vitamins is currently under investigation in sub-groups of the CKD population, especially in those with known risk factors for cardiovascular disease.

Currently, 60 mg of vitamin C daily is recommended for patients with CKD to offset increased loss in the urine or into dialysate (19, 20). However, vitamin C is an important serum and intracellular antioxidant, and its beneficial effects include inhibition of lipid peroxidation, which has been associated with damage to cellular macromolecules, inactivation of antioxidant enzymes and increased risk of atherosclerosis. Maintenance dialysis patients show both vitamin C deficiency and oxidative stress, and there is interest in the effects of higher doses of vitamin C on

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Table 1. Recommendations for daily vitamin supplementation in patients with Chronic Kidney Disease (CKD) (19)

Vitamin	Pre-dialysis CKD	Chronic HD/PD
Vitamin C	60 mg/day	60 mg/day
Vitamin B1	1-5 mg/day	1-5 mg/day
Vitamin B2	1.2-1.7 mg/day	1.2-1.7 mg/day
Niacin	13-19 mg/day	13-19 mg/day
Vitamin B6	5 mg/day	10 mg/day
Vitamin B12	2 mcg/day	2 mcg/day
Folic acid	1 mg/day	1 mg/day
Vitamin B5	4-7 mg/day	4-7 mg/day
Biotin	30-100 mcg/day	30-100 mcg/day
Vitamin A	none	none
Vitamin E	unknown	unknown
Vitamin K	none	none

oxidant levels in these patients (21). While short-term oral vitamin C supplementation (250 mg three times per week for 2 months) does not modify markers of oxidative stress in maintenance HD patients, the effects of higher vitamin C doses over a longer time period remain to be investigated.

Vitamin E, a fat-soluble antioxidant and scavenger for oxygen-free radicals, has also been investigated for its potential protective effects against lipid peroxidation in patients with CKD. Studies of vitamin E status in both pre-dialysis and maintenance dialysis patients show contradictory results and have reported decreased, normal and elevated serum vitamin E levels (22). When combined with the lipid-lowering agent atorvastatin calcium (Pfizer Inc. New York, NY), 800 IU alpha-tocopherol given once daily for 12 weeks decreased oxidisability of low-density lipoprotein (LDL) in patients undergoing maintenance dialysis therapy (23). However, alpha-tocopherol administered daily for 12 months to hemodialysis patients increased levels of anticardiolipin antibodies, which have been linked with higher incidence of thrombosis and progression of atherosclerosis (24).

Serum levels of lipoprotein (a), a risk factor for atherosclerotic heart disease, increase as renal failure progresses, but can be lowered by the administration of niacin derivatives (25). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Clinical Practice Guidelines for Managing Dyslipidemias in Chronic Kidney Disease also recommend niacin as a therapeutic agent (26). Niacin therapy may be considered in this population when lifestyle changes including nutritional intake, weight reduction, physical activity and abstinence from alcohol fail to reduce triglycerides to < 500 mg/dL (< 5.65 mmol/L) or when lifestyle changes in combination with statin therapy are insufficient to reduce LDL to < 100 mg/dL (< 2.59 mmol/L). Recommended dose ranges for niacin are shown in Table 2. Although no data is available in the CKD population, studies in the general population show that niacin reduces triglycerides by 20-50%, reduces LDL by 5-25% and increases high-density lipoprotein (HDL) by 15-35%. Adverse effects of niacin therapy may include flushing, hyperglycemia and hepatotocixity.

Table 2. Niacin dose for treatment of dyslipidemias in Chronic Kidney Disease (CKD) (26)

Agent	Dose (g/day)
Immediate release	1.5 - 3.0
Extended release	1.0 - 2.0
Sustained release	1.0 - 2.0

Hyperhomocysteinemia (total homocysteine > 1.89 mg/L [14.0 µmol/L]) is present in over 85% of patients with moderate to severe CKD (Stages 3 to 5), promoting endothelial changes that accelerate atherosclerosis and contribute to cardiovascular disease (27-30). Folic acid, which is essential for homocysteine metabolism, reduces homocysteine levels in the non-CKD population when given as an oral supplement. Ten MHD patients (mean age 37±2 years) who received 10-20 mg folic acid daily for 6 months experienced a significant drop in homocysteine levels, suggesting that relatively large doses of folic acid may decrease cardiovascular disease risk factors (31).

A meta-analysis of 12 randomized trials of vitamin supplements in the non-renal population was directed to determine the optimal folic acid dose to lower homocysteine levels and to evaluate the additional effects of vitamins B6

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and B12 (32). According to this investigation, a daily dose of 0.5 to 5 mg folic acid reduced homocysteine levels by 25%, and 0.5 mg vitamin B12 daily produced an additional 7% reduction in homocysteine levels. Vitamin B6 (mean dose 16.5 mg) did not have any significant effect on homocysteine level.

Similar studies have recently been conducted in maintenance dialysis patients, and high doses of folic acid, vitamin B6 and vitamin B12 for 6 months normalized homocysteine levels in 72% of patients undergoing CAPD (33). In a prospective, randomized, double-blind trial of 60 stable MHD patients (mean age 68 ±13 years), participants received either a daily renal multivitamin containing 5 mg folic acid, 10 mg vitamin B6 and 0.4 mg vitamin B12 or supraphysiological doses of these vitamins (15 mg, 100 mg and 1 mg respectively) (34). The renal multivitamin elicited a 23.6% reduction in homocysteine levels after one month and a 28.3% reduction after 6 months; homocysteine levels remained stable thereafter and only 12% of participants had normal homocysteine levels after 12 months of therapy. Supraphysiological doses of folic acid, vitamin B6 and vitamin B12 did not improve outcomes.

Although the trace elements iron, selenium and zinc are commonly deficient in patients with CKD, there is no data to support routine use of oral supplements (22). While oral iron is the cheapest and easiest means of supplementing iron intake, poor absorption from the gut combined with gastrointestinal side effects and interaction with calcium-based phosphate binders limits effectiveness of these supplements.

Selenium is essential for the activity of the enzyme glutathione peroxidase, which helps to protect cells against oxidative damage (22). Low selenium levels have been linked with lipid peroxidation abnormalities in patients undergoing MHD. While low serum selenium levels in MHD patients have been attributed to poor dietary protein intake and losses through the dialyzer membrane, a recent investigation of selenium status in this population reported plasma selenium concentration within the normal range (1.51-1.70 µmol/L [119-134 µg/L]) (22,35). A liquid formula supplemented with selenate maintained serum concentrations in the normal range in stable, well-nourished MHD patients who were adequately dialyzed; plasma selenium concentrations were higher in this group of patients than in those who did not receive the supplement (35). MHD patients who received erythropoietin (EPO) and an oral selenium supplement showed increased glutathione peroxidase activity in their red blood cells as well as significantly higher serum selenium concentrations when compared with MHD patients who received EPO therapy alone (36). Nevertheless, selenium supplementation in patients with CKD requires caution because of its potential toxic effects.

Low levels of zinc have been reported in pre-dialysis patients with CKD and in patients undergoing maintenance dialysis therapy (22). Zinc deficiency has been linked to poor appetite and altered sense of taste and smell, which occur commonly in renal failure. While hemodialysis has minimal effects on serum zinc levels, red blood cell zinc levels are lower in CAPD patients than in those receiving MHD. In a study designed to determine the effects of zinc supplementation on serum zinc and cholesterol levels, 20 MHD patients received either 50 mg elemental zinc or placebo for 90 days and completed 2-day food records (one dialysis day and one nondialysis day) at the beginning and end of the study (37). Patients who received the zinc supplement showed significant increases in serum zinc and total cholesterol levels, both of which had been low at the onset of the study. In addition, mean reported energy intake in the zinc supplemented group increased from 1385 to 1682 kcal/day. On the contrary, CAPD patients who received 100 mg element zinc daily showed no improvement in nutritional status after 90 days, despite increased serum zinc levels (38).

Applications for the renal nutrition professional

Patients with CKD report that they obtain information about dietary supplements mainly from physicians and printed materials (16). However, patients are not routinely asked about dietary supplement use by either physicians or nurses, and there is limited availability of educational materials on vitamin and mineral supplements for patients with CKD (1,39,40). Nutrition professionals may be best suited to identify use of dietary supplements when they collect information on a patientís nutritional intake during the nutritional assessment phase of medical nutrition therapy (1).

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Wide variability in vitamin and mineral intake is evident in patients with CKD (13-16). For this reason, the renal nutrition professional must gather detailed information about vitamin and mineral intake from food, and use of vitamin and mineral supplements. Since intake of vitamins B2, niacin, B6 and vitamin E correlates with mean daily calorie and protein intake, nutrition counseling to increase both calories and protein could significantly increase vitamin and mineral intake (14).

Table 3 shows the vitamin and mineral contents of supplements formulated to meet the requirements of patients with CKD. The need for vitamin and mineral supplementation depends on the extent of renal insufficiency, type and adequacy of renal replacement therapy, the patient's nutritional status and prescribed medications (14,15,22). Recommendations regarding vitamin supplementation should therefore be used as guidelines that may be individualized according to the patient's nutritional intake and medical status. Antibiotics can decrease absorption of vitamins A, D, K, B12, B6, folic acid and zinc while fecal loss of most vitamins increases with laxative use (41). Patients taking anticonvulsants may have impaired absorption or

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Table 3. Comparison of vitamin supplements formulated for patients with Chronic Kidney Disease (CKD)

Product	Vit C mg	B1 mg	B2 mg	Niacin mg	B6 mg	B12	Folic Acid	B5 mg	Biotin mcg	Vit A IU	Vit E IU	Zn mg	Se mcg
Dialyvite®	100	1.5	1.7	20	10	6 mcg	1 mg	10	300	-	-	-	-
Dialyvite® with Zinc	100	1.5	1.7	20	10	6 mcg	1 mg	10	300	-	-	50	-
Dialyvite® 3000	100	1.5	1.7	20	25	1 mg	3 mg	10	300	-	30	15	70
Diatx®	60	1.5	1.5	20	50	1 mg	5 mg	10	300	-	-	-	-
Diatx® Zn[a]	60	1.5	1.5	20	50	2 mg	5 mg	10	300	-	-	25	-
Nephrocaps®	100	1.5	1.7	20	10	6 mcg	1 mg	5	150	-	-	-	-
Nephron FA®[b]	40	1.5	1.7	20	10	6 mcg	1 mg	10	300	-	-	-	-
Nephrovite®	60	1.5	1.7	20	10	6 mcg	0.8 mg	10	300	-	-	-	-
Nephrovite® Rx	60	1.5	1.7	20	10	6 mcg	1 mg	10	300	-	-	-	-
NephPlex® Rx	60	1.5	1.7	20	10	6 mcg	1 mG	10	300	-	-	12.5	-
PS Nephro-Aid	60	1.5	1.5	20	20	1 mg	950 mcg	10	300	3000	100	-	-
RenaPlex®	60	1.5	1.7	20	10	6 mcg	0.8 mg	10	300	-	-	12.5	-
Renax	50	3.0	2.0	20	16	12 mcg	2.5 mg	10	300	-	35	20	70

[a] Diatx® Zn also contains 1.5 mg copper gluconate.
[b] Nephron FA® also contains 200 mg ferrous fumarate.
Dialyvite®, Dialyvite® with Zinc and Dialyvite® 3000 are registered trademarks of Hillestad Pharmaceuticals, Woodruff, WI.
Diatx® and Diatx® Zn are registered trademarks of PamLab, LLC, Covington, LA.
Nephrocaps® is a registered trademark of Fleming & Company Pharmaceuticals, Fenton, MO.
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PS Nephro-Aid is a registered trademark of Physician Select Vitamins LLC, Houston, TX.
RenaPlex® is a registered trademark of NutriMed Labs, Irving, TX.
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utilization of vitamins B6, B12, folic acid, D and K, and anti-gout medications increase excretion of vitamin B2. Patients with CKD who are prescribed diuretics have increased urinary excretion of vitamin B1 and zinc, and lipid-lowering agents decrease vitamins A, D, K and B12 (41). Corticosteroids increase the need for vitamins C, D, B6 and folic acid, and for zinc while levels of folic acid, vitamin C and vitamin B12 are impacted by anti-inflammatory agents.

Higher doses of niacin, vitamin B12 and folic acid than are currently recommended may be needed to decrease risk factors for cardiovascular disease in patients with CKD (26,33, 34). While renal failure is also accompanied by oxidative stress, currently available data provides limited evidence for the benefits of antioxidant supplements in this population (42). As more investigations are performed on the pharmacologic use of vitamins in patients with CKD, recommendations regarding supplementation in these patients are likely to change (19). Therefore, it is important for the nutritional professional to balance each individual patient's needs with the current scientific evidence available when making dietary supplement recommendations and intervention in the CKD population.

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The results of the *Compensation & Benefits Survey of the Dietetics Profession 2005* are in and the news is good: dietetics salaries are on the rise. The survey, conducted May 11 to July 5, 2005 by Readex Research on behalf of the American Dietetic Association (ADA) and the Commission on Dietetic Registration (CDR), collected demographic, employment, and compensation data from over 12,000 dietetics professionals. Both registered dietitians (RDs) and dietetic technicians, registered (DTRs) reported wage gains equal to or greater than inflation, an 8.2% increase over the median income levels reported in the previous compensation survey, conducted in 2002. It was also found that dietetics professionals receive benefits packages considered among the best in any profession.

In order to understand the factors that contribute to the level of compensation dietetics professionals receive, the survey collected specific information about education levels, work experience, job responsibilities, ADA membership, and practice area. First, it was found that higher education isnít just its own reward, as advanced degree earned brought with it a substantial increase in median income, with a jump of $5,000 per year a Masterís degree, and a median increase of over $20,000 a year for a Doctoral degree. Dietetics professionals also earn more than the national average for each degree they earn. When it comes to work experience and responsibility, the more you have, the more you earn. Not surprisingly, income continues to rise as experience is gained. Compensation also increases with greater responsibility, as management of both employees and budgets brings significant gains in pay. Earnings varied according to practice area, and the survey identified those areas experiencing the most growth as well as those with the highest salaries, with private practice being the most lucrative. Last but not least, the survey found that ADA members had a median income more than $3,000 higher than non-ADA members.

The complete, 190-page *Compensation & Benefits Survey of the Dietetics Profession 2005* contains much more detailed, in-depth analysis of salaries, including compensation analysis for 48 different positions in dietetics and salary calculation worksheets to help dietetics professionals determine their own fair level of compensation. To order your own copy of the survey, call ADA at 800-877-1600, ext. 5000 or visit the online catalog at www.eatright.org/catalog.

CERTIFICATE OF COMPLETION

Dietary Supplement use in Patients with Chronic Kidney Disease

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