

Nutrition Intervention for Advanced Stages of Diabetic Kidney Disease

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■ **IN BRIEF** For the goals of reducing diabetic kidney disease (DKD) onset and progression, approaches to nutritional therapy are a subject of much debate. This article discusses selected nutrients that have a role in affecting DKD outcomes and introduces application of newer, individualized concepts for healthful eating, as supported by clinical evidence relevant to patients with DKD. Selected aspects of management of advanced DKD are also reviewed.

Nutrition goals for adults with diabetes include obtaining control of blood glucose, blood lipids, and hypertension; achieving a healthy body weight; and preventing systemic complications of diabetes (1). When applied to individuals with diabetic kidney disease (DKD), these targets become harder to achieve, complicated by the interrelationships between and effects of individual macro- and micronutrients on kidney function, renal hemodynamics, albuminuria, disease progression, associated metabolic complications, and nutritional status. Disease-specific dietary modifications for DKD are recommended for protein, carbohydrates, fat, and electrolytes, with the latter dependent on individual kidney function (2–4). Weight management and physical activity are also recognized as modifiable risk factors for the prevention and management of both diabetes (1,3) and DKD (2,4) and their shared associated complications of cardiovascular disease (CVD), dyslipidemia, and hypertension (1–4). Therefore, prescriptive exercise is an important adjunctive aspect of nutritional therapy for individuals with DKD.

Although nutrition intervention for DKD does require calculation of macro- and micronutrient and electrolyte requirements, a growing body of evidence suggests that specific dietary patterns of intake may confer additional therapeutic benefit (5–7). Application of these principles may enhance nutrition intervention for DKD (8). This article reviews a sampling of the studies that have provided the evidence base for current protein recommendations, briefly reviews important concepts pertaining to carbohydrate and fatty acid intake for DKD, and identifies dietary patterns associated with improved clinical outcomes for chronic disease. Applying such dietary patterns to individuals with advanced stages of DKD will be an important area for future research.

Dietary Protein and DKD

Both the quantity and the quality of protein and amino acids have been identified as important for maintenance of adequate nutritional status in CKD, irrespective of original cause (9). Determining optimal dietary protein intake in DKD is further complicated by the fact that kidney disease confers unique metabolic abnormalities that can include alterations in mineral metabolism,

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metabolic acidosis, anemia, vitamin D deficiency, loss of lean muscle mass, and susceptibility to malnutrition. The relationship between dietary protein and DKD is less definitive with regard to the effects of the amount and source of protein on kidney outcomes, and specifically on preventing and impeding the progression of DKD. It is well accepted that excessive dietary protein intake is associated with a worsening of kidney function, increased albuminuria, and CVD mortality (10–14).

A significant number of studies have investigated the role of dietary protein restriction in this regard, but the literature is inconclusive (15–26). Results are limited because of variability in important aspects of study methodology, including test diet composition, outcome measurements of kidney function, diet adherence, and retrospective awareness that more than one diet variable was manipulated in the study. Table 1 summarizes these and additional study components that contribute to the inconclusive results from the literature. The following sampling of studies reiterates the mixed results and study limitations.

Zeller et al. (15) provided an example of the effects of a diet low in protein and phosphorus in patients with type 1 diabetes. The researchers compared the effects of a diet lim-

ited in protein (0.6 g/kg ideal body weight), phosphorus (500–1,000 mg), and sodium (2,000 mg) to a control diet containing ≥ 1.0 g/kg of protein per day and 1,000 mg of phosphorus in 35 patients with type 1 diabetes and evidence of nephropathy over 37 months. At baseline, mean 24-hour urinary protein was 4.2 g in the control group and 3.1 g in the intervention group, and mean iothalamate clearance (mL/s/1.73 m²) was 0.772–0.813 in both groups. Kidney function was evaluated by iothalamate and creatinine clearance measurement at 3- to 6-month intervals. Diet adherence was verified for protein intake by urinary excretion of urea nitrogen and for phosphorus by 24-hour urinary excretion of phosphorus. Results revealed that patients on the low-protein, low-phosphorus diet had a significantly slower rate of decline in iothalamate ($P < 0.03$) and creatinine clearance ($P < 0.03$) from baseline to the end of the study than those on the control diet. Final mean 24-hour urinary protein excretion was 196 mg lower than baseline in the intervention group compared to 1,024 mg more than baseline in the control group. This study evaluated not only protein, but also phosphorus and sodium restrictions, which may confer independent benefits to kidney outcomes.

A meta-analysis of nutrition studies completed by Kasiske et al. (24) evaluated 13 randomized, controlled trials and reported that the effect of dietary protein restriction (GFR decline in treatment minus control) was greater in patients with than in those without diabetes (5.4 mL/min/year [95% CI 0.3–10.5] to 10.5 mL/min/year, $P < 0.05$), with a nonsignificant trend for a greater effect with each additional year of follow-up. The studies in this meta-analysis, while encouraging, had short durations and small sample sizes.

Hansen et al. (16) evaluated a low-protein (0.6 g/kg/day) versus a usual-protein diet for 4 years in 82 patients with type 1 diabetes and progressive diabetic nephropathy. Outcome parameters measured were end-stage renal disease (ESRD) or death. Actual protein intake during the follow-up period was 0.89 g/kg/day in the low-protein group and 1.02 g/kg/day in the usual-protein group. ESRD or death occurred in 10% of patients on the low-protein diet and 27% of patients on the usual-protein diet ($P = 0.042$). The relative risk of death or ESRD after baseline adjustment for CVD was 0.23 for patients on the low-protein diet ($P = 0.01$). Notably, although the protein intake goal of 0.6 g/kg/day was not achievable, the actual protein intake level

TABLE 1. Examples of DKD Dietary Protein Study Limitations

Parameters Pertaining to Kidney Disease and Kidney Care	Diet and Nutrition Parameters
<ul style="list-style-type: none"> • Patient mix varies: type 1 versus type 2 diabetes • Stage of kidney disease varies: early to late (i.e., CKD stages 2–4) • Provision of standards of care varies: some studies report on management of hypertension and lipids, whereas others do not • Method of measuring kidney disease progression varies • Method of measuring albuminuria, and reporting of such measures, vary: urinary protein or albumin: creatinine ratio often are not reported • Sample size varies • Lengths of treatment are short: no long-term studies 	<ul style="list-style-type: none"> • Adherence to test diets was not always achieved • Lack of management of other macronutrients when dietary protein intake decreased; therefore, unclear if studies truly evaluated only the effect of adjustment of dietary protein intake • Composition of dietary protein not reported other than in studies specifically evaluating vegetarian or plant proteins • Nutritional status parameters often not addressed • Composition of dietary fats not identified • Composition of dietary carbohydrate not identified • Studies not always reporting dietary phosphorus and sodium intake in subjects

resulting in a beneficial outcome was modest.

A study completed by Meloni et al. (18) did not find beneficial effects of a low-protein diet. Patients with either type 1 ($n = 32$) or type 2 ($n = 37$) diabetes followed a low-protein diet (0.6 g/kg/day) or a free diet for 12 months. All patients started the study with stable blood pressure on calcium channel blockers or ACE inhibitors and stable nutritional status. GFR (mL/min/1.73 m² by ⁵¹Cr-EDTA clearance) was 45 in the free diet group and 43.9 in the low-protein diet group. At end of study, GFR was not significantly different between groups (39.3 mL/min/1.73 m² in the free diet group vs. 38.8 mL/min/1.73 m² in the low-protein diet group). The calculated protein intake in the low-protein group was 0.68 g/kg/day compared to 1.39 g/kg/day in the free diet group. Mean energy and phosphorus intake were also reported as significantly lower in the low-protein group than in the free diet group. The low-protein group lost a mean of 2.6 kg ($P < 0.01$) compared to stable weight in the free diet group. These changes were accompanied by significant decreases in serum albumin and pre-albumin levels. Of note, constituency of diets in terms of protein, carbohydrates, and fat sources was not described. Weight loss indicates an imbalance of macronutrient intake, but nutrition therapy for adequacy of overall intake was lacking.

Additional studies and meta-analyses have been completed with conflicting results. Dussol et al. (20) found no benefit of a 2-year low-protein diet (0.8 g/kg/day) compared to usual protein intake (1.2 g/kg/day) on GFR or albumin excretion rates. Intake of other dietary macronutrients was not controlled. A meta-analysis of low-protein diets and diabetic nephropathy completed by Pan et al. (17) also reported no significant benefit of a low-protein diet on renal function in patients with type 1 or type 2 diabetes and nephropathy.

Some studies have suggested a beneficial effect of plant-based protein sources on kidney disease and DKD outcomes (27–30). It is not clear whether the effects of plant-based protein diets are the result of their amino acid composition, carbohydrate sources, fatty acid intake, total calories, enhanced intake of antioxidants and phytonutrients, percentage of calories from each macronutrient group, decreased phosphate intake levels, or other undefined interactions between nutrients or nutrient-gene interactions. Further research pertaining to the potential of vegetarian and plant-based protein sources is warranted.

The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) (2), Kidney Disease Improving Global Outcomes (KDIGO) (4), and the American Diabetes Association (ADA) (3) have completed extensive reviews of the literature pertaining to dietary protein intake and DKD and have evaluated the evidence base for clinical guidelines for this macronutrient (1–4). The KDOQI guidelines recommend a target protein intake of 0.8 g/kg/day for people with DKD stages 1–4, with a Grade B evidence rating (2). The KDIGO guidelines suggest a dietary protein intake of 0.8 g/kg/day in adults with diabetes and a GFR <30 mL/min/1.73 m² with appropriate education, with a Grade 2c evidence rating (4). The ADA recommends usual dietary protein intake, with a Grade A evidence rating (3). Both KDOQI and KDIGO recommend avoidance of high levels of protein intake, defined as >20% of kcal from protein (2) and >1.3 g/kg/day for individuals with CKD (4), respectively.

Carbohydrate and Fat Recommendations

Whole-grain carbohydrates, fiber, and fresh fruits and vegetables are recommended as part of a healthy diet for individuals with CKD and DKD (1,9). The number of portions

and specific food selections from these food groups often need to be limited in advanced stages of DKD because of the high potassium and phosphorus content of many carbohydrate foods (9). Carbohydrates are an important contributor of lower-protein calories. Whether an increase in the percentage of calories from complex carbohydrate food choices would result in improvement in the outcomes of DKD and its accompanying comorbid conditions is not known.

Research inquiries pertaining to dietary fat were initially in relation to reducing risk factors for CVD and improving lipid profiles (31). However, additional properties unique to the omega-3 and omega-9 fatty acids have also been recognized, including anti-inflammatory mechanisms and a favorable modification of cellular function (32–34). These observations spurred continued interest in the inclusion of such fatty acid-derived foods within the diet for DKD. There is a growing body of evidence suggesting beneficial effects of omega-3 fatty acids on albuminuria in diabetic nephropathy (35,36). However, definitive conclusions to support specific dietary recommendations are not yet available. The general recommendation for DKD is to include omega-3 and omega-9 fatty acids as part of total dietary fat intake, while decreasing intake of saturated fats and food sources of trans fatty acids (2).

Sodium Restriction

Dietary sodium restriction in individuals with CKD has been shown to affect blood pressure, proteinuria, volume status, immunosuppressant therapy, and efficacy of antihypertensive medications (37). Dietary sodium recommendations for individuals with DKD do not currently differ from those for people with CKD. The recommended range of dietary sodium intake for individuals with DKD is 1,500–2,300 mg/day (1,2,4). To successfully limit sodi-

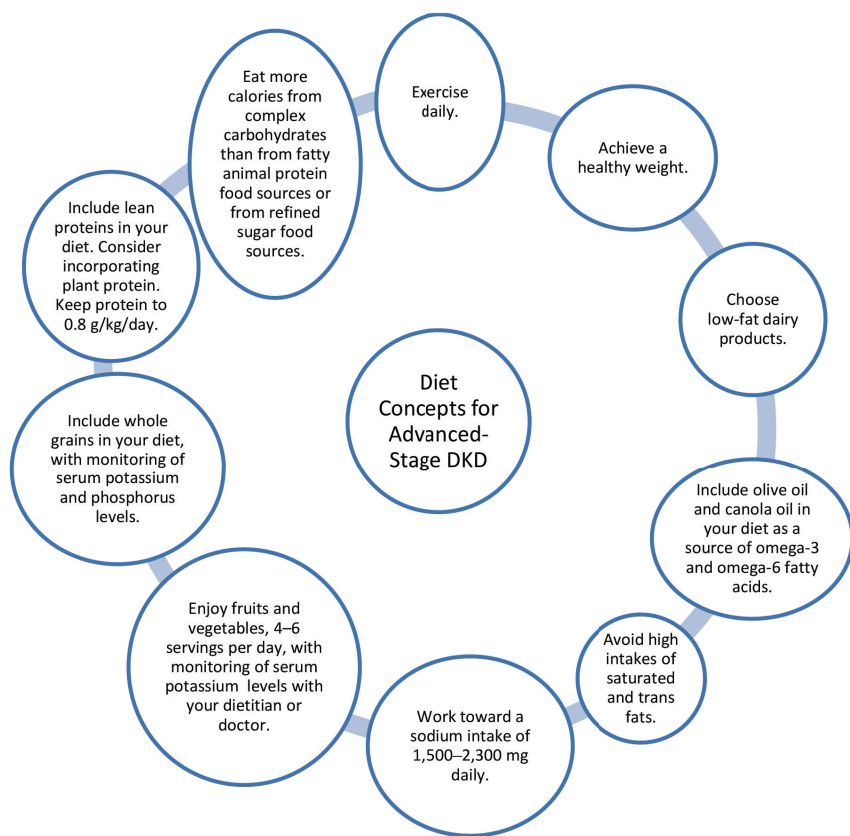


FIGURE 1. Diet concepts for advanced-stage DKD.

um intake to this range, nutrition recommendations include increasing dietary intake of fresh cooked foods and reducing intake of fast foods and highly processed food products (2,9).

Examining Dietary Patterns of Intake

A growing body of evidence suggests that focusing on diet patterns of intake, rather than on intake of individual nutrients per se, offers an insightful approach to examining and identifying the role of diet in chronic disease (5–7). Both the Mediterranean (6) and DASH (Dietary Approaches to Stop Hypertension) (5) diets include enhanced intake of whole-grain (complex unrefined) carbohydrates, fruits, vegetables, and plant proteins, including nuts, seeds, and beans. Although fish is included in these diets, intake of other animal proteins and whole-fat dairy products is decreased compared to the Western

diet (7). The Mediterranean diet also incorporates olive oil and includes red wine. Focusing on dietary patterns in conjunction with principles of healthy lifestyle management is a new approach to dietary management of DKD.

Whether a healthy diet pattern will affect albuminuria, DKD progression, CVD outcomes, or weight management is unclear. However, the current Western dietary pattern, enriched in animal protein, fat (total and saturated), sodium, sugar, and calories, is strongly associated with many chronic diseases and exacerbation of disease risk factors (i.e., hypertension, obesity, and CVD) (7). Clinical trials are needed to ascertain the efficacy, role, and safety of the Mediterranean dietary pattern for individuals with DKD with regard to both kidney outcome parameters and nutritional status.

Figure 1 provides a visual concept of patterns of eating that have been associated with improvement in blood pressure, weight, and cardiovascular risk factors. Incorporation of diet pattern concepts into the process of specific food selections within each food group may facilitate adherence to guidelines and enhance the potential therapeutic benefits of nutrition intervention. Individualization of nutrition therapy is essential for the optimal care of people with DKD. For all published recommendations and guidelines, it is important that individuals achieve and maintain adequate nutritional intake of nutrients, as well as a healthy BMI, to enhance risk reduction.

Management of Advanced Stages of CKD

Given the inherently progressive nature of CKD, people with DKD, if they survive through other complications of diabetic macro- and microvascular disease, often experience the advanced stages of CKD, with eGFR falling to <30 mL/min/1.73 m² (38). Renal replacement therapy, usually in the form of maintenance dialysis treatment, will be needed for these people to survive the ravages of uremia with progressive worsening kidney function. Type 2 diabetes is the leading cause of ESRD in the United States and many countries globally, and approximately half of the 450,000 dialysis patients in the United States have ESRD secondary to type 2 diabetes (39). These patients have a high prevalence of comorbid conditions, a high hospitalization rate, low levels of health-related quality of life, and an excessively high mortality rate of 15–20% per year, mostly because of CVD events (39).

Observational studies in dialysis patients, including those with type 2 diabetes, have not found a significant association between traditional CVD risk factors and mortality. The existence of a paradoxical or reverse association, in which obesity, hypercholesterolemia, and hypertension

appear to confer survival advantages, has been described (40,41). The time discrepancy between the competing risk factors (i.e., over-nutrition [long-term risks] vs. under-nutrition [short-term risks]) may explain the overwhelming role of protein-energy wasting, inflammation, and cachexia in causing this so-called “reverse epidemiology” (42–45). Other comorbidities of advanced-stage CKD, such as secondary hyperparathyroidism, appear to have similar associations in patients with and without diabetes for complications, health care costs, and survival (46).

Role of Glycemic Control in ESRD

The role of improved glycemic control in ameliorating the exceedingly high mortality rate of dialysis patients with diabetes is unclear. The treatment of diabetes in ESRD patients is challenging given changes in glucose homeostasis, the questionable accuracy of glycemic control metrics, and the altered pharmacokinetics of glucose-lowering drugs by kidney dysfunction, the uremic milieu, and dialysis therapy (40).

Up to one-third of dialysis patients with type 2 diabetes may experience falling glucose levels, with A1C levels <6%. The causes and clinical implications of this observation have not been determined, although under-nutrition and limited substrate availability are likely operative factors (38,47–49). Conventional methods of glycemic control assessment are confounded by the laboratory abnormalities and comorbidities associated with ESRD. Similar to more recent approaches in the general population, there is concern that intensive glycemic control regimens aimed at normalizing glucose may be harmful in ESRD patients. There is uncertainty surrounding the optimal glycemic target in this population, although recent epidemiological data suggest that A1C ranges of 6–8% or 7–9% are associated with increased survival rates among dialysis patients

with diabetes (46). This association exists in both hemodialysis (47,48) and peritoneal dialysis patients with diabetes (49). Pre-transplant glycemic control is also associated with post-transplant outcomes in kidney transplant recipients with diabetes (50).

New-Onset Diabetes After Transplantation

New-onset diabetes after transplantation (NODAT) is a clinically important and unique condition defined as persistence of hyperglycemia (meeting the criteria for diabetes) beyond initial hospitalization in transplanted patients without preexisting diabetes. It occurs in 15–25% of patients who undergo organ transplantation (51,52).

Immunosuppressive regimens, including steroid and calcineurin inhibitors (in particular, tacrolimus), have been implicated in the development of NODAT (51). Calcineurin inhibitors may lead to pancreatic cell apoptosis with resultant decline in insulin secretion; they may also interfere with the calcineurin/nuclear factor of activated T-cell pathways, leading to distortion of skeletal muscle glucose uptake (52). Post-transplant increases in appetite and weight gain may also play a role in the development of NODAT.

NODAT independently increases the risk of cardiovascular events and infection and shortens kidney allograft longevity and patient survival (53). Judicious glycemic control and other preventive and management strategies have been suggested, including resting the pancreatic β -cells by administering insulin during the period immediately after transplantation and instituting intensive lifestyle modification after kidney transplantation to lower the incidence of NODAT (53).

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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