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Diet and Diabetic Kidney Disease: Plant Versus Animal Protein

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Abstract

Purpose of Review—The goal of this review is to present an overview of the evidence on the effectiveness of plant-based diets in delaying progression of diabetic kidney disease (DKD).

Recent Findings—The ideal quantity of dietary protein has been a controversial topic for patients with DKD. Smaller studies have focused on protein source, plant versus animal, for preventing progression. Limited evidence suggests that dietary patterns that focus on plant-based foods, those that are lower in processed foods, or those that are lower in advanced glycation end products (AGE) may be useful in prevention of DKD progression.

Summary—Increasing plant-based foods, incorporating diet patterns that limit processed foods, or potentially lowering AGE contents in diets may be beneficial for dietary management of DKD. However, dietary studies specifically targeted at DKD treatment are sparse. Further, large trials powered to assess outcomes including changes in kidney function, end-stage kidney disease, and mortality are needed to provide more substantial evidence for these diets.

Keywords

Nephropathy; Protein; Advanced glycation end products; Dietary patterns

Introduction

Diabetic kidney disease (DKD) is a major cause of end-stage renal disease (ESRD) in the USA [1]. Approximately 50% of ESRD worldwide is due to diabetes [2]. With the rising incidence of type 2 diabetes, it becomes critical to attempt to halt progression of diabetes to DKD and ESRD. Prevention of diabetes is the most dependable way to prevent DKD and therefore its progression [3•]. A few studies have investigated effects of dietary interventions in patients specifically with respect to DKD progression; these studies are the focus of this review. However, for aspects of diets that are not studied in detail with respect to DKD

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Compliance with Ethical Standards

Conflict of Interest Ranjani N. Moorthi, Colby J. Vorland, and Kathleen M. Hill Gallant declare that they have no conflict of interest.

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progression, we have turned to studies on the effects of diet on prevention of diabetes and CKD progression individually, which is rationalized by the two facts that (1) DKD is best prevented by primary prevention of diabetes and (2) a large proportion of the CKD population has diabetes.

Role of Low-Protein Diets in DKD Progression

The impact of dietary protein restriction in DKD is a much debated topic. Two small randomized controlled trials (RCTs) showed no differences in average rate of decline of glomerular filtration rate with a low-protein diet versus a higher protein diet [8, 9]. One of these studies randomized 69 subjects with type 1 or 2 diabetes, to a low-protein diet of 0.6 g/kg versus a “free protein” diet for 12 months [4], while the other randomized 63 type 1 and 2 diabetics to 0.8 g/kg/day versus a “usual protein” intake for a 2-year follow-up period [5]. In contrast, in a RCT of 82 type 1 diabetic patients (mean GFR 68 ml/min) randomized to a low protein (0.6 g/kg/day) versus a usual protein intake group for 4 years, the rate of progression to ESRD was 27% in the usual protein group and 10% in the low protein group ($p = 0.042$) [6]. Similar to the RCT above, a meta-analysis of 13 studies of low-protein diets in DKD found that a low-protein diet was associated with a significant improvement in GFR of 5.8 ml/min/1.73 m^2, but this effect was only noted in those with high compliance and there was no effect of low-protein diets on proteinuria [7]. However, a Cochrane meta-analysis that included 9 RCTs and 3 pre-post studies found that a low-protein diet lowered the risk of progression of DKD, but not significantly [8]. Studies of patients with type 1 and type 2 diabetes were pooled in this analysis; the studies were variable in duration and only one was powered to the outcome of ESRD.

Taken together, a definitive conclusion on the impact of protein-restricted diets on DKD progression is difficult given the variability in study duration, incomplete compliance [8], likely confounding by other treatment (e.g., RAAS blockade) and lack of hard outcomes. Furthermore, these diets pose a significant burden on patients [9] and are associated with a higher risk of malnutrition [4]. Given the quality of data available, the NKF-KDOQI guidelines do not recommend extremely low-protein diets, but instead recommend moderate restriction in protein intake to 0.8 g/kg/day in those with DKD (grade B recommendation, i.e., “moderately strong evidence”) as well as avoidance of greater than 20% of caloric intake from protein [10].

Plant-Based Diets: Getting the Names Right

“Plant-based diet” is a catch-all term that includes a variety of dietary approaches. Broadly, plant-based sources of protein can be soy based or non-soy based. Soy-based diets decrease urine albumin excretion [11, 12], possibly from the actions of isoflavones. The isoflavone genistein is a tyrosine kinase inhibitor that inhibits endothelial cell proliferation. It also inhibits nitric oxide, a potent vasodilator, and this may explain the lower renal blood flow and reduction in hyperfiltration associated with soy-based diets [12, 13]. However, different soy varieties have different amounts of isoflavones [14], potentially contributing to heterogeneity in results in studies of outcomes of kidney disease progression in diabetes.

There are also studies of “vegan” diets which refer to an exclusively plant-based diet, as well as “vegetarian” which usually refer to plant-based diet with intake of dairy, but with exclusion of seafood and meat.

Interventional Studies of Plant-Based Diets in DKD

Interventional studies of plant-based diets in DKD progression are limited by small sample size and short duration. There is also significant heterogeneity in baseline GFR in the study populations and in types of dietary interventions. In a study by Stephenson et al. [15], 18 patients with type 1 diabetes were enrolled for a crossover trial for a soy-based diet versus a control diet, where the intervention periods lasted 8 weeks each with a washout [15]. The mean GFR at the start of the study was 151.9 ± 8.2 ml/min. On the soy diet, approximately 50% of the 1.34 ± 0.11-g/kg protein was from soy sources, and the remainder from other plants (~28% non-soy sources, such as grain) and animal sources. Animal-based protein was derived from poultry and limited meat items. At the end of the soy diet period, the GFR was lower than at baseline as well as at the end of the control period ($p = 0.02$). This was interpreted as a decrease in glomerular hyperfiltration on a predominantly plant-based protein diet in patients with type 1 diabetes with early DKD. Of note, there were no changes in urine albumin excretion. This study has limited generalizability due to small size and high dropout rate [15].

In 34 subjects with type 2 diabetes and DKD (mean serum creatinine of less than 1.5 mg/dl and a 24-h urine albumin excretion less than 2 g/day), soy protein intake was compared to the dairy protein casein. Subjects were placed on 8 weeks of each diet containing a protein-restricted diet of 1.2 mg/kg/day of either soy protein or casein with wash-out periods in between. Urine albumin excretion was increased 16.3 mg/g in the casein period ($p = 0.002$) and decreased 20.3 mg/g by soy protein consumption ($p < 0.001$). Changes in urinary albumin excretion were independent of changes in glycemic control, ascertained by glycosylated hemoglobin [16].

A single meal intervention study in healthy subjects and in patients with type 2 diabetes, stratified according to albumin excretion rate, was performed by Nakamura et al. [17]. One gram per kilogram of soy protein was compared with 1 mg/kg tuna fish protein meals. In the group with the highest albumin excretion rate, GFR decreased significantly after a single tuna fish meal but was unaffected by soy protein intake. Albumin excretion rate did not change with either meal. The authors ascribe the effect on the GFR to elevations in amino acids in the circulation that are different after tuna fish consumption versus soy protein intake. It may be that a single cooked fish meal increased the serum creatinine without changing kidney function [18].

Why Might Plant-Based Diets Be Beneficial?—Phosphorus, Sodium, and Fiber

The mechanisms by which plant-based diets may reduce DKD progression may be related to the form of phosphorus, a reduction in blood pressure by decreasing sodium, an increase in fiber leading to improved glycemic control, or from bioactive compounds in soy protein-

based diets such as isoflavones, as described above. Plant-based sources of protein tend to have the less bioavailable form of phosphorus as phytate compared to organic phosphorus found in processed foods as well as in animal sources of protein [19]. Two studies of plant-based diets in CKD showed lower urinary phosphorus excretion in CKD [19, 20]. Azadbakht et al. [21] studied the effect of 7 weeks of a 65% vegetarian diet, compared to a 70% animal-based protein source in subjects with DKD (serum creatinine 1–2.5 mg/dl and with macroalbuminuria) in a crossover design. In addition to the decrease in albuminuria, serum phosphorus was lower by 0.2 ± 0.3 mg/dl in the vegetarian diet compared to 0.03 ± 0.2 mg/dl in the animal protein diet [21]. Restriction of dietary sodium in diabetics decreases systolic and diastolic blood pressure [22] and increases the blood pressure lowering efficacy of medications, such as irbesartan as well as other ARBs [23]. Additionally, diets rich in fiber may improve insulin sensitivity and glycemic control [24]. This was demonstrated in an observational study in a Japanese diabetes registry of 4399 subjects where increased dietary fiber consumption was associated with decreased albuminuria and/or eGFR <60 ml/min/1.73 m^2. Putative mechanisms for this include the effect of fiber in increasing peripheral insulin sensitivity as well as in decreasing absorption of glucose from the GI tract [25].

Overall Dietary Patterns and DKD Progression

Apart from a focus on single nutrients like protein, the overall dietary pattern and distributions of macronutrients may lead to favorable outcomes in DKD. Additionally, specific macronutrient distributions may be associated with improvement in lipid control, glycemic control, weight loss, and thereby lower cardiovascular risk in patients with diabetes. A diet pattern that is high in processed foods, red meat, and sugar has been shown to be associated with increased insulin resistance [26]. Observational studies show relationships between diet patterns and DKD progression. One of the largest of these observational studies included 6213 participants with type 2 diabetes (a subset of the ONTARGET trial with n = 25,620) with GFR and albumin excretion assessed at study onset and end [27•]. Patients with healthier eating patterns had significantly lower odds of developing CKD or its progression and lower odds of albuminuria. Urine sodium excretion <3 and >7 g/day and decreased intake of potassium and green leafy vegetables was associated with mortality in those with CKD. From a patient perspective, it is easier to shift dietary eating patterns from an “unhealthy” to a “healthier” overall pattern than convert form a predominantly animal protein diet to a vegan diet. This is especially so for patients with type 2 diabetes in whom conflicting advice is provided in an effort to address each macrovascular complication. Though the ONTARGET study was observational, given the large sample size it provides a reasonable overview of the benefits of healthy eating patterns, which include a significant intake of plant-based foods.

Other dietary patterns that have been studied most include the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), ketogenic, and US Dietary Guidelines (as measured by the mAHEI) (Table 1). The Mediterranean diet has beneficial effects on diabetes incidence and glycemic control in randomized trials [28, 29] and prospective cohorts [30]. It also improves kidney function, but not albuminuria, over 1 year in community dwelling elderly with cardiovascular risk factors [31]. A meta-analysis

comparing Mediterranean diets with other dietary patterns (low fat, Paleolithic) was performed in overweight patients at risk for (or with) type 2 diabetes. Mediterranean diet decreased glycosylated hemoglobin levels significantly compared to “usual” care. Interestingly, the Mediterranean diet was not significantly more beneficial than the Paleolithic diet with respect to glycemic control [32].

The DASH diet effectively reduces blood pressure in RCTs [33], an important risk factor in the development of kidney and cardiovascular diseases [34]. Adherence to Dietary Guidelines is associated with reduced CKD incidence or adherence [27•]. Finally, a meta-analysis of ketogenic diet RCTs suggest that it is effective at reducing diastolic blood pressure and some other cardiometabolic risk factors, but increases LDL-c and does not improve glycemic control [35]. With the exception of the ketogenic diet, these dietary patterns share the characteristic of being heavily plant-based and can be used to individualize patient diets to promote adherence as suggested by the American Diabetes Association [36].

Dietary Advanced Glycation End-Products and Progression of DKD

Advanced glycation end products (AGEs) form as a result of non-enzymatic glycation and oxidation of proteins or lipids after contact with aldose sugars. Common AGEs include N^{ε}-carboxymethyl-lysine (CML) and methylglyoxal (MG). AGEs are formed endogenously, particularly in the hyperglycemic milieu of diabetes, or are exogenously consumed from food sources [37, 38]. They alter tissue structure and function, for example, by reducing nitric oxide production, LDL clearance, and by forming AGE-AGE cross-links in the extracellular matrix. AGEs can induce inflammation by signaling via the receptor for advanced glycation end products (RAGE). Alternatively, AGE binding to AGE-receptors 1, 2, and 3 (AGE-R1, -R2, -R3) promotes AGE clearance [37].

Endogenous AGE production is elevated in diabetes, and animal experiments have further implicated them in the pathogenesis of diabetes, suggesting they may contribute to both the initiation and progression of the disease [39, 40•]. Approximately 10% of dietary AGEs are absorbed, and are either cleared by the kidneys or incorporated into tissues [41]. In healthy humans, urinary AGE levels return to baseline by 24 h post-consumption of an AGE-rich meal. However, in patients with diabetes, this is extended to 48 h [41]. Patients with DKD have higher serum and tissue AGE levels, proportional to severity of kidney disease, likely due to their impaired renal AGE clearance [41, 42].

Restriction of dietary AGEs presents a novel approach in the prevention of DKD. In the NOD and db/db mouse models of diabetes, a low-AGE diet reduced serum AGEs, urinary albumin excretion, and glomerular volume and increased survival, compared to standard chow [43]. Human trials specific to DKD are lacking, but emerging evidence suggests that limiting dietary AGEs may lead to improved outcomes in CKD and diabetes, by reducing inflammation and improving lipid control and glucose homeostasis (Tables 2 and 3). It is not clear whether improving these parameters would decrease progression of DKD, and this remains an important future research question in the field.

Plant-Based Dietary Patterns and Cooking Methods to Lower AGEs

Dietary AGEs exist naturally in foods, particularly those of animal origin. They are also generated from heating (e.g., grilling, broiling, roasting, searing, frying) during food preparation and processing [38]. Thus, focusing on plant-based diets along with altering cooking techniques may be effective approaches to lower dietary AGEs. Uribarri et al. analyzed dietary AGEs from common foods and concluded that reducing dietary AGEs may be best achieved by shifting diet patterns toward higher intakes of whole grains, vegetables, fruits, legumes, fish, and low-fat dairy products and lower intakes of solid fats, fatty meats, full-fat dairy products, and highly processed foods [38], which is most consistent with a DASH or Mediterranean style diet pattern [44]. These diet patterns fit within recommendations from the American Diabetes Association [36, 44]. Cooking methods that preserve moisture such as stewing, steam-cooking, boiling, or poaching generate fewer AGEs compared, e.g., broiling, frying, or roasting. Such preparations reduce AGEs by 50% or more. Because current trials have been performed by simple modifications of food preparation, the combination of this and modifying dietary patterns on DKD progression may be of clinical interest. Establishing ranges for human dietary AGE consumption that may reduce the risk for diabetes and/or kidney disease progression require further research.

Caveats of Study Design Common to Studies of Diets in DKD

Surrogate Outcomes

Interventional studies in patients with diabetes would ideally be powered to assess hard clinical endpoints, such as death or ESRD (defined as dialysis initiation or kidney transplantation). However, these outcomes take years to occur. In reality, studies of diets are expensive to conduct and ensuring patient compliance and follow-up for prolonged periods in a study situation is extremely difficult. Surrogates for development and progression of DKD that are commonly used in clinical research studies are GFR and slope of creatinine changes, albuminuria or proteinuria. Whether albuminuria is an appropriate surrogate for hard clinical end points of dialysis initiation, death, or even of a “softer” endpoint of GFR decline is controversial [45, 46]. Due to the limited availability of data on impact of diets on endpoints of death and end stage kidney disease in diabetes, we have reviewed studies that use assumed surrogates above.

Concomitant Therapies, Effect Modifiers, and Confounders

In a complex disease process such as DKD, concomitant therapies or lifestyle changes may confound or modify the association between prescribed study diets and DKD progression. For example, renin angiotensin aldosterone system (RAAS) antagonism is known to slow DKD progression [23]. However, the dose and type of prescribed RAAS inhibitors may change during a diet study. Dietary sodium restriction (a part of study diets in some cases) may potentiate the effect of RAAS inhibition. Physical activity levels may vary during a study and confound the effect of diet on outcomes by independently affecting risk factors such as glycemic control.

Conclusion

Decreasing the rate of progression of DKD is an extremely important goal in patients with diabetes to decrease the incidence of ESRD. Diet and pharmaceutical agents are synergistic in their actions on albumin excretion and GFR loss. The focus in the area of diet impact on DKD progression is shifting from ideal protein quantity to the type of protein consumed, e.g., animal versus plant. Though the evidence is from a variety of non-homogenous small studies, it appears that dietary patterns with more plant-based foods and fewer processed food items, such as the DASH and Mediterranean diets, would slow progression of DKD. Diabetes is associated with an increased endogenous AGE burden. Diets restricted in AGEs need to be studied in interventional trials in DKD to determine if the decreasing inflammation and favorable changes in glycemic or lipid control translate to a slowing of DKD progression. Studies of low AGE and plant-based dietary patterns need to be studied over longer periods of time in larger populations, using outcomes of hard clinical endpoints.

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Table 1

Diet definitions

Diet	Definition	Reference
Mediterranean diet pattern	High • Olive oil, legumes, unrefined cereals, fruits, vegetables Moderate-to-high • Fish Moderate • Dairy products (mostly as cheese and yogurts) • Wine Low • Meat and meat products	Martinez-Gonzalez et al. (2009) [47]
DASH	High • Fruits, vegetables, low-fat dairy products, whole grains, nuts, legumes, seeds, fish, poultry (lean meats) Low • Red meat, sweets and added sugars, total fat, saturated fat, cholesterol	NHLBI (2006) [48]
Ketogenic diet	<50 g carbohydrate daily, with increases in fat and protein	Paoli et al. (2013) [49]
Dietary Guidelines (modified Alternate Healthy Eating Index; AHEI)	High • Fruits, vegetables, nuts and soy protein, white meat, whole grains Moderate • Alcohol Low • Red meats, trans fat	McCullough et al. (2002) [50]
Paleolithic	High • Fruits, vegetables, nuts, seeds, lean meats Low • Dairy, grains, processed foods	Katz and Meller (2014) [51]

Table 2

Effect of a low-AGE diet on inflammation markers in diabetes and/or kidney disease in humans

Reference	Disease	Intervention length	TNF-α (ng/mg)	NF-kB p65	CRP (mg/dl)	PAI-1 (ng/ml)	VCAM-1 (ng/ml)	8-Isoprostane	SIRT1	AGE-R1	RAGE (mRNA)	Malondialdehyde
Uribarri et al. 2003, Peppa et al. 2004 [52, 53]	CKD (renal failure, diabetic and non-diabetic)	4 weeks	↔		↓	↓	↔					
Vlassara et al. 2009 [54]	CKD stage 3	4 weeks	↓				↓	↓		↑[a]	↓	
Vlassara et al. 2002 [55]	Diabetes	2 weeks	↓		↔		↓					
		6 weeks	↓		↓		↓					
Uribarri et al. 2011 [56]	Type 2 diabetes	4 months	↓	↓				↓	↑[b]	↑[b]	↓	
Luévano-Contreras et al. 2013 [57]	Type 2 diabetes	6 weeks	↓									↓

[a] mRNA only

[b] mRNA and protein

Table 3

Effect of a low-AGE diet on glucose and lipid metabolism in diabetes and/or kidney disease in humans

Reference	Disease	Intervention length	Insulin (μU/ml)	Fasting glucose (mmol/l)	HOMA	HbA1c	Adiponectin (μg/ml)	Leptin (ng/ml)	Blood pressure (mmHg)	AGE LDL (units/ml)	LDL-C (mmol/l)	HDL-C (mmol/l)	Triglycerides (mmol/l)	Chloesterol (mmol/l)
Vlassara et al. 2002 [55]	Diabetes	2 weeks		↔		↔			↔	↓	↔	↔	↔	↔
		6 weeks		↓		↔			↔	↓	↔	↔	↔	↔
Cai et al. 2004[a] [58]	Diabetes	6 weeks								↓				
Uribarri et al. 2011 [16, 39]	Type 2 DM	4 months	↓		↓		↑	↓						
Luévano-Contreras et al.	Type 2 DM	6 weeks	↔	↔	↔	↔						↔	↔	↔

[a]Extension of Vlassara et al. (2002)