Risks and Benefits of Different Dietary Patterns in CKD

Shivam Joshi, Kamyar Kalantar-Zadeh, Philippe Chauveau, and Juan Jesus Carrero

Food has the potential to cause and exacerbate many lifestyle diseases. Or it can be used to prevent and treat illnesses like primary hypertension, the metabolic syndrome, and insulin resistance. In parallel, there is also a growing body of evidence of the role of diet in the treatment of kidney disease and its ensuing complications. Popular diets for this purpose have included low-carbohydrate diets, including the ketogenic diet, and higher carbohydrate diets like Mediterranean diets and other plant-based dietary patterns. Low-carbohydrate diets have not shown harm in patients with kidney disease and may benefit a select few. Mediterranean diets have an established record of cardioprotective benefits but also may be beneficial for the kidney. Intermittent fasting has benefits for metabolic health, but limited research exists on the risk or benefit for patients with kidney disease. Plant-based diets, especially those that are lower in protein, may slow kidney disease progression, mitigate uremia, and delay dialysis initiation. Although each dietary pattern has its unique pros and cons, most healthful dietary patterns favor the inclusion of whole, unprocessed foods, preferably from plant-based sources. In this perspective, we discuss the risks and benefits of major popular diets to help guide health care professionals in treating patients with kidney disease.

Complete author and article information provided before references.

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The increasing use of plant-based and ketogenic diets for the treatment of comorbidities, such as obesity, diabetes, and hypertension, has created interest regarding the utility of these diets in patients with chronic kidney disease (CKD). Are these diets safe, and if so is there any additional benefit to using them? Although evidence in some areas is still limited, it has undergone significant growth in recent years. In this article, we review the evidence on consuming a low-carbohydrate diet (including a ketogenic diet) or plant-based diet (including Mediterranean diets) or intermittent fasting by patients with CKD who are not receiving kidney replacement therapy. For patients with a kidney transplant, we refer readers to Cyrino et al[1] for an excellent review of the topic.

Western Diets

The modern Western diet is rich in animal-based foods and processed/ultraprocessed foods, resulting in a high intake of saturated fats, refined carbohydrates, and salt. This diet has been linked to metabolic disorders, including obesity, hypertension, diabetes, cardiovascular diseases (CVD), and other associated conditions, including cognitive impairment and emotional disorders.[2] We will discuss recent the evidence on selected downsides of this diet, but for a fuller examination we refer readers to Hariharan et al[3] for a review on the potential harms of Western diets on CKD.

A high consumption of meat and animal protein has been associated with the risk of incident CKD and kidney failure.[4] Underlying mechanisms may relate to the effect of protein intake on hyperfiltration.[5] Some studies have suggested that animal protein may cause more hyperfiltration than nonanimal protein.[6] In addition, fermentation of protein in the gut by proteolytic bacteria results in the production of uremic toxins, which may lead to oxidative stress, inflammation, and progressive loss of kidney function.[7]

A recent study in mice with CKD suggested that limiting the intake of aromatic amino acids (tyrosine, tryptophan, and phenylalanine, which are primarily present in animal protein) could be as effective as limiting overall protein intake in mitigating kidney damage through decreased production of uremic toxins. The study compared 3 different diets for 6 weeks and observed that both a low-protein diet and a diet low in aromatic amino acids reduced proteinuria, kidney fibrosis, and inflammation compared with a normal protein diet. However, the greatest reduction in uremic toxin production was achieved by the diet low in aromatic amino acids.[8]

Western diets are typically high in added sugars and sweeteners. The consumption of added sugar, soft drinks, and sodas has been associated with the risk of albuminuria, incident CKD, and loss of estimated glomerular filtration rate (eGFR).[9] The underlying mechanisms have not been well described but may involve the promotion of obesity, diabetes, or hypertension and the increase in uric acid levels, all of which are risk factors for CKD. Limiting fructose intake lowers blood pressure and inflammation. In a crossover trial, 28 patients with CKD stages 2-3 were switched from a regular (60 g/24 h) to a low (12 g/24 h) fructose diet for 6 weeks, then resumed their regular diet for another 6 weeks. The main intervention to reduce fructose intake was limiting the consumption of soft drinks. The low-fructose diet resulted in significant reductions in blood pressure, insulin, and inflammatory molecules. No changes were seen in uric acid levels.[10]

The consumption of ultraprocessed foods has increased globally in recent decades, especially in Western diets. These foods are usually energy dense: high in saturated fat, sugar, salt, and additives, and low in dietary fiber and vitamins. The primary motivation of ultraprocessing is to create products that are ready-to-consume and hyperpalatable with a longer shelf-life.[11] Studies have

consistently found associations between these foods and the risk of cardiometabolic diseases, cancer, and premature death.[12] Two studies have evaluated the associations between diets rich in ultraprocessed foods and the risk of kidney outcomes. In a prospective Dutch cohort of over 78,000 individuals with normal kidney function, 38% of the total food intake came, on average, from ultraprocessed foods. During a follow-up of 3.6 years, the participants in the highest quartile of ultraprocessed food consumption experienced a higher risk of a composite kidney outcome of incident CKD or a relative eGFR decline of more than 30%. This was observed regardless of their macro- or micronutrient intake or diet quality.[13] In another study from the ARIC cohort, there was a linear relationship between ultraprocessed food intake and the risk of developing CKD. The authors estimated that substituting 1 serving per day of ultraprocessed foods with minimally processed foods was associated with a 6% lower risk of CKD (hazard ratio, 0.94 [95% CI, 0.93-0.96], $P < 0.001$).[14]

Low-Carbohydrate and Ketogenic Diets

There has been recent interest in advising a carbohydrate intake less than the recommended range for CKD patients to preserve kidney function by addressing underlying conditions such as obesity and diabetes. The ketogenic diet, a type of low-carbohydrate diet, is of interest because it metabolizes fat as the body's main energy source instead of glucose, thereby reducing blood glucose concentrations. Clinical trials assessing low-carbohydrate diets in CKD are limited. Therefore, this guidance is inferred from studies in the general population.

Is Eating a Low-Carbohydrate Diet Beneficial for CKD?

Table 1 defines carbohydrate intake patterns based on the percentage of daily carbohydrate consumption derived from various studies.[15] It is unclear whether these diets benefit body weight control and cardiovascular risk. A Cochrane review meta-analyzed 61 trials that randomized 6,925 participants, who were either overweight or living with obesity, to either low-carbohydrate (<45% of total energy) or balanced-carbohydrate weight-reducing diets (>45% of total energy).[16] They reported little to no difference in weight loss (mean difference, −0.93 [95% CI, −1.81 to 0.04] kg; $I^2 = 40\%$) between these diets over the span of 1 to 2 years. The presence of type 2 diabetes mellitus (T2DM) did not modify this conclusion, nor was glycemic control affected. Although some highly adherent individuals had a remarkable response to the diet, in published trials the benefits mostly waned after 12 months.[17-19]

Table 1. Dietary Classification of Carbohydrate Consumption

Carbohydrate Diet Classification	Percent of Daily Energy Intake From Carbohydrates
Very-low-carbohydrate diet	<10% carbohydrates
Low-carbohydrate diet	10%-25% carbohydrates
Moderate-carbohydrate diet	26%-44% carbohydrates
High-carbohydrate diet	≥45% carbohydrates

Based on information in Oh et al[15]; percentages based on total calories.

The 2020 KDOQI nutrition guideline recommends a low protein intake (0.55-0.60 g/kg/d without diabetes, 0.6-0.8 g/kg/d with diabetes) for patients with CKD stages 3-5 to retard the progression to kidney failure and prevent uremic symptoms.[20] Low-carbohydrate/high-protein diets may conflict with this recommendation because excess protein intake can promote kidney injury[21] due to hyperfiltration and increased intraglomerular pressure.[5] Clinically, this may be observed as a rise in estimated or measured GFR.

In a randomized, crossover feeding trial of 163 participants without CKD, those consuming a low–glycemic index diet, a low-carbohydrate diet, or both had an increase in eGFR based on cystatin C of 1.9 to 4.5 mL/min/1.73 m^2 compared with those eating a reference diet that was high in carbohydrates and glycemic index.[22] The increase in GFR has been shown by other studies.[23] The possibility of harm is suggested in a community-based observational study of 1,797 persons who were observed for a mean of 6.1 years and responded to a food frequency questionnaire.[24] In those adhering to a low-carbohydrate/high-protein diet, there was an association with a higher risk of developing CKD (odds ratio, 1.48 [95% CI, 1.03-2.15]).

Trials, however, generally fail to observe signs of kidney injury. In a meta-analysis of randomized controlled trials (RCTs) of up to 2 years' duration there was nearly no change in eGFR in those consuming low-carbohydrate diets compared with those eating control diets of higher carbohydrate content.[25] Another meta-analysis of RCTs of patients with diabetes and normal eGFR suggested no difference in any measure of kidney function with this diet intervention.[26] Both meta-analyses noted that the RCTs considered carbohydrate intakes ranging from <4% to 43% at initiation, reported substantial dropout rates, and had nonadherence issues that may have confounded the effects reported. Admittedly, the short duration of the trials (up to 2 years) may have limited their ability to detect long-term kidney damage.

All in all, current evidence suggests little benefit to low-carbohydrate diets in managing CKD and its complications. There is a possibility of harm by high protein intake, but the short duration of these trials prevents us from establishing a clear cause and effect. It is possible to consume a low-carbohydrate diet that also limits protein consumption to amounts recommended in the KDOQI guideline by increasing the fat content of the diet. However, when taken to the extreme this type of diet can become a ketogenic diet.

Is Eating a Ketogenic Diet Beneficial for CKD?

The ketogenic diet generally draws at least 70% of calories from fat with no more than 15% of calories from carbohydrates. The remaining calories come from protein, but protein excess is avoided so that gluconeogenic substrates are not created. Table 2 lists the macronutrient breakdowns of several ketogenic diets used in studies as effective treatments for diseases such as epilepsy, cancer, and Alzheimer disease.[27] Ketogenic diets recently have also become popular for the treatment of obesity and T2DM. Meta-analyses of mostly short-term (<12 months) trials have shown substantial decreases in glycemic markers and weight.[28] However, it may be difficult to adhere to this dietary pattern for long: trials report high dropout rates and/or increased consumption of carbohydrates that prevent ketosis.[17] A meta-analysis of long-term trials (with a duration of >12 months) randomizing individuals to very-low-carbohydrate ketogenic diets (<10% of energy from carbohydrates) or low-fat diets (<30% of energy from fat) showed that those on the ketogenic diet achieved a statistically significant but small reduction in weight of 0.9 kg.[19] No difference was seen in glycemic control at 12 months between both diets.

Two short-term trials evaluated these diets in CKD patients. Goday et al[29] conducted a RCT of 89 participants with T2DM over 4 months and showed no difference in kidney function markers between those consuming a ketogenic diet and a control, low-calorie diet (500-1,000 kcal/d). Another nonrandomized, prospective study by Bruci et al[30] of 92 patients, 38 with CKD stage 2 and 54 with normal kidney function, following a very-low-calorie ketogenic diet (450-800 kcal/d) for approximately 3 months also showed no difference in serum creatinine or eGFR. However, in a separate analysis of those with an eGFR of 60-89 mL/min/1.73 m^2, the participants had a statistically significant increase in eGFR from 76.32 to 82.21 mL/min/1.73 m^2.[30] Although the researchers attributed the amelioration in eGFR to the diet itself, this effect was not seen in the Goday et al[29] study, which also studied patients with a similar eGFR; the change may have been explained by other causes such as an increase in dietary animal protein consumption (baseline protein consumption not reported) or a reduction in dosage of medications that inhibit the renin-angiotensin-aldosterone system (one-third of those on antihypertensive medications had a reduction in dosage or discontinuation of an antihypertensive medication).

Table 2. Macronutrient Contents of Various Ketogenic Diets

	Percent of Total Calories		
Macronutrient Ratio[a]	Fat	Protein	Carbohydrate
Classic keto (4:1)	90%	6%	4%
Modified keto			
(3:1)	87%	10%	3%
(2:1)	82%	12%	6%
(1:1)	70%	15%	15%
MCT oil (1.9:1)	50%/21%[b]	19%	10%
Low glycemic index treatment (2:3)	60%	28%	12%
Modified Atkins diet (0.8:1)	65%	29%-32%	3%-6%

Reproduced in modified form courtesy of Beth Zupec-Kania from Table12 of Zupec-Kania et al[72]; original content ©2018 The Charlie Foundation.
[a]Macronutrient ratio is the relationship between the grams of fat to the grams of protein plus carbohydrate (fat:protein + carbohydrates). In a 4:1 ratio there are four times the amount of fat in grams as there is protein and carbohydrate.
[b]50% MCT/21% LCT, where MCT refers to medium-chain triglycerides and LCT refers to long-chain triglycerides.

Ketogenic diets may be of interest in the treatment of polycystic kidney disease (PKD) because they have shown to reduce the growth of cysts in animal models.[31] Human trials in this area are in progress. A feasibility study of a plant-focused ketogenic diet was conducted with 20 participants who had autosomal dominant PKD with an eGFR range of 24-94 mL/min/1.73 m^2.[32] Favorable results were reported, including average decreases in body weight by 5.6% and fasting blood glucose levels by 16.5%, along with an average increase in eGFR of 8.6%.

These diets, however, may be associated with health risks. Observational studies have associated the consumption of saturated fat and animal fat, which are prominent features of traditional ketogenic diets, with an increase in albuminuria.[33,34] Specific concerns regarding the use of ketogenic diets include an increased net acid load, with possible worsening of metabolic acidosis, and the risk of nephrolithiasis, which have all been reported in pediatric patients using the ketogenic diet for the treatment of epilepsy.[17,35]

Other potential risks of this diet include the potential to cause dyslipidemia and hyperlipidemia and an increased risk of mortality in observational studies.[36,37] The increase in low-density lipoprotein and apolipoprotein B is concerning in patients with CKD, which is a population already at an increased risk for CVD.[37] In order to preserve cardiovascular health, it has been recommended that the carbohydrate and fat intake come from unprocessed, fiber-rich, plant sources.[38] Replacing animal-based foods with unprocessed plant foods may have a favorable effect on lipids by increasing polyunsaturated and monounsaturated fat content and reducing saturated fat and natural trans fat.[37] Indeed, a plant-based, low-carbohydrate diet has been shown to cause weight loss and improve CVD risk factors in patients without CKD.[39] Animal-based, low-carbohydrate diets may be undesirable in those with CKD for several other reasons as previously mentioned.[4] However, it should be noted that there currently is no evidence-based research in favor of or against a plant-based, low-carbohydrate diet in CKD.

Intermittent Fasting

Intermittent fasting is a term used to define alternating eating and fasting patterns implemented on a regular schedule (Table 3). Intermittent fasting has increased in

Table 3. Classification of Various Types of Intermittent Fasting

Types of Intermittent Fasting	Description
Alternate-day or periodic fasting	Alternating days of no food or beverage with days of food and beverage
Modified fasting	In each week, 20%-25% of daily energy needs consumed for 2 nonconsecutive fasting days, with ad libitum eating for the 5 remaining days
Time-restricted feeding or time-restricted eating	Ad libitum eating within a specific time frame of the day, usually ≤12 h/d, paired with fasting for balance of the day
Religious fasting	Various fasting regimens conducted for a religious or spiritual purpose

Based on information in Patterson and Sears.[73]

popularity for the treatment of obesity and insulin resistance. The benefits of intermittent fasting are attributed not only to reductions in caloric intake but also the use of fatty acids for ketone bodies.[40] A systematic review and meta-analysis of patients without CKD found significant reductions in body mass index, fasting glucose level, insulin resistance, and fat mass in those consuming an intermittent fasting diet compared with those on a control diet.[41]

Few clinical trials have been conducted with intermittent fasting and CKD, though several observational studies have been reported on CKD patients who fast for Ramadan. In these studies, kidney function has been noted to improve, decrease, or stay the same.[42] The mixed results may be due to the uncontrolled nature of the studies and the different conditions of the study (location, time of the year, and daily duration of fasting). Those observing Ramadan often also abstain from water and medications during fasting hours, which may induce dehydration and acute kidney injury, among other problems.[43] Because some who fast during Ramadan have experienced a decline in eGFR, some experts do not recommend the adoption of fasting that excludes water or medications in those with advanced CKD.[42] However, when including the appropriate use of water and medications, intermittent fasting may provide several important health benefits.

Plant-Based Diets

Plant-based diets emphasize the consumption of plants and may or may not include small/moderate amounts of meat, fish, seafood, eggs, and dairy. Thus, vegan, vegetarian, and other patterns of diet with moderate consumption of animal foods—such as Mediterranean or Dietary Approaches to Stop Hypertension (DASH) diets—are all to be considered plant-based.[4,44] These types of diets have many potential and actual benefits for the prevention and treatment of CKD, a topic that has been discussed in detail previously.[4,44] New trials continue to support the benefit of these diets in CKD. Among 140 patients with resistant hypertension (21% of whom had CKD), randomization for 4 weeks to a DASH-type diet and exercise or a single counseling session resulted in a small lowering of blood pressure (by 10 mm Hg) and improvement on a number of cardiovascular biomarkers.[45]

In clinical practice, plant foods are often restricted due to to hyperkalemia, which may not be evidence based.[46] A recent study evaluated the information provided to patients in 24 handouts, booklets, and webpages from public health agencies in Canada and the United States.[47] All these information sources emphasized the avoidance of fruits and vegetables, while about half discussed other sources of dietary potassium such as dairy products, whole grain, coffee, or chocolate. Only one-third of the materials reviewed mentioned potassium additives and ultraprocessed foods, which have been shown to increase potassium content in foods by 3-fold.[48] However, despite this emphasis on restricting potassium, most studies fail to observe strong associations between dietary and serum potassium.[46]

Recently, a randomized, crossover, 4-week feeding study of 29 patients with CKD stage 3 compared 2 DASH diets, which emphasize plant foods over animal foods, with different potassium contents.[49] Both diets observed KDOQI guideline recommendations and had similar macro- and micronutrient content except for potassium content (100 vs 40 mmol potassium per day). On the high-potassium diet, mean serum potassium increased by 0.21 mmol/L ($P = 0.003$) compared with the low-potassium diet, driven by 2 confirmed instances of hyperkalemia. In both instances, the participants had a history of hyperkalemia (an exclusion criteria of the study) and/or usage of medications known to cause hyperkalemia (such as tacrolimus or an angiotensin-receptor blocker). This study thus suggests that it is possible to increase the intake of potassium-containing plant foods in persons with CKD, but hyperkalemia may occur in those with a history of hyperkalemia and/or those using medications that are associated with hyperkalemia.

More importantly, studies have failed to find strong associations between dietary potassium and adverse clinical outcomes. The largest of these studies came from over 8,000 patients on hemodialysis.[50] Potassium intake was assessed by food frequency questionnaires and stratified into quartiles. Across quartiles of greater dietary potassium, the intake of fruits, vegetables, and legumes was incrementally higher than the intake of fish, meat, or eggs. Dietary potassium intake was not associated with all-cause mortality and did mediate the association between plasma potassium and death. The limitations of food frequency questionnaires (such as over/underreporting as well as the inability to estimate inorganic potassium from additives or fully capture demineralization of cooking methods) may add an element of confounding, but these findings support the hypothesis that stringent plant food restrictions may not be needed for most patients with CKD, in agreement with KDOQI recommendations.[17,20,44,46]

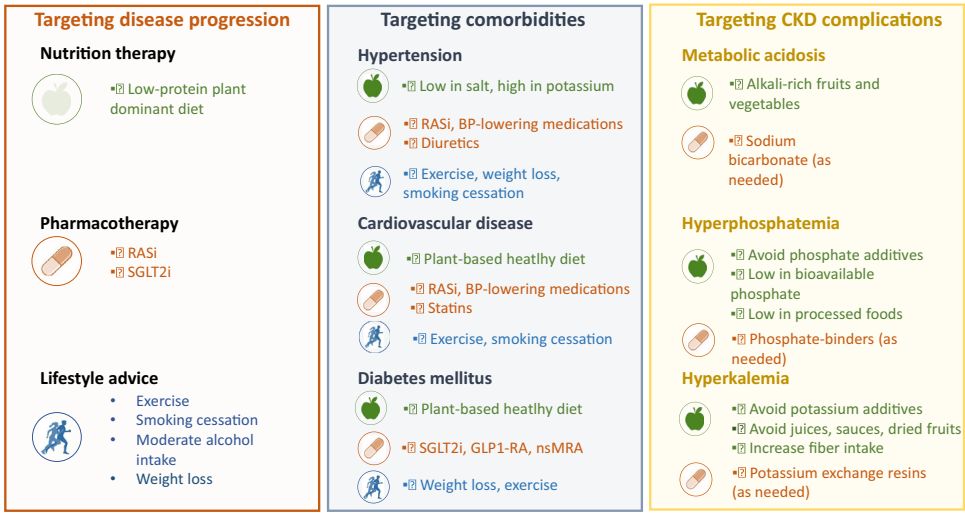

Figure 1. Complementary use of nutrition, lifestyle, and pharmaceutical therapies for the treatment of CKD and its complications. Abbreviations: BP, blood pressure; RASi, renin-angiotensin-system inhibitors; SGLT2i, sodium/glucose cotransporter 2 inhibitors.

Mediterranean Diets

A Mediterranean dietary pattern exemplifies a healthy plant-based diet. In clinical trials, it has been demonstrated to improve lipid profile, reduce cardiovascular risk,[51] and ameliorate oxidative stress, inflammation, and insulin resistance.[52,53] In addition, meta-analyses of prospective cohorts and trials have demonstrated its effectiveness for the prevention and treatment of T2DM.[54]

Moderate consumption of wine and olive oil differentiates the Mediterranean from other plant-based diets. Polyphenol compounds found in red wine exert beneficial effects on vascular disease and together with extra-virgin olive oil provide more than 30 phenolic compounds with anti-inflammatory, antioxidant, and vasculoprotective properties.[55] The consumption of oleic acid from olive oil has been associated with a lower risk of death, CVD morbidity, and stroke.[56,57] The benefits of the plant foods consumed in this dietary pattern cannot be overlooked, but the beneficial effects have also been attributed to the low amounts of meat consumed.[58,59]

A meta-analysis of general population studies found that every 1-point greater adherence to the Mediterranean Diet Scale was associated with a 10% lower odds for developing CKD.[60] Studies in patients with manifest CKD also suggest better outcomes, such as reduced risk of progression toward kidney failure, favorable cardiometabolic markers, and lower mortality.[53,61-63] We should be cognizant that patients adhering to a Mediterranean dietary pattern may have other healthful behaviors—including having better food literacy[64] and higher

Table 4. Risks and Benefits of Different Dietary Patterns in CKD

Dietary Pattern	Benefits	Risks
Low-carbohydrate diets	• Avoids high glycemic index foods • Improved weight loss and glycemic control for those who are highly adherent	• High protein content may cause hyperfiltration in CKD • Inclusion of saturated and trans fats from animal sources may increase the risk of CVD • Long-term adherence may be difficult • Most RCTs show the benefits of weight loss and glycemic control waning after 12 months • Replacing carbohydrates with animal protein may increase acid load
Intermittent fasting	• Improved weight loss and glycemic control	• Electrolyte imbalance and a decrease in kidney function may result from dehydration and refraining from medications
Plant-based diets	• Benefits for multiple chronic diseases • High alkaline load • High in fiber and antioxidants • Possible reduction in eGFR decline and proteinuria	• Patients and providers are often unfamiliar with these diets • Hyperkalemia or protein deficiency could result from poor planning

Abbreviations: CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RCT, randomized controlled trial.

physical activity—that limit the interpretations from observational studies.[65]

Trials demonstrating the benefits of this diet in the general population may serve to inform the choices of patients with CKD. The PREDIMED trial demonstrated the benefits of Mediterranean diets for primary CVD prevention, but the CORDIOPREV study expanded these benefits to secondary CVD prevention and CKD progression.[51,66] In the CORDIOPREV study, 1,002 patients with coronary heart disease were randomized to a Mediterranean diet (35% fat, <50% carbohydrates) or a low-fat diet (28% fat, >55% carbohydrates). Those in the Mediterranean diet also had 10% more calories from monounsaturated fatty acids. The mean eGFR was 89.2 mL/min/1.73 m^2. Those in the Mediterranean diet group had a mean eGFR decline rate that was 1.58 mL/min/1.73 m^2 lower than the low-fat diet group during the 5 years of follow-up evaluation.

Special Considerations: Food Insecurity and the Cost of Healthy Diets

In Western countries like the United States, many residents are faced with food insecurity, defined as an inadequate availability of nutritionally adequate and healthy foods. Much of this is a product of counterintuitive food policies that subsidize unhealthy food at multiple levels and create relatively higher costs for healthy food.[67] Food insecurity is associated with an increased risk of CKD but is considered to be a modifiable risk factor.[68]

Although the data on diets for patients with CKD are limited, several insights can be gleaned from analyses of other healthy, primarily plant-based, diets. The EAT-Lancet reference diet, a universal reference diet that is healthy for both humans and the planet, is mainly plant-based and was found to cost a median of USD $2.84 per day using retail price data from 2011 for 744 foods in 159 countries (adjusted for inflation this amounts to USD $3.71 presently).[69] In lower and middle-income countries, the consumption of plant-based diets can be substantially less costly than a Western diet.[70] It is likely that a global movement toward the consumption of healthy, plant-based diets (and away from animal-based diets) has the potential to feed an additional 4 billion people.[71]

Conclusion

Diet and lifestyle changes should be seen as complementary to existing medical treatments, including pharmacotherapy (Fig 1). Like medical treatments, each diet has its own unique benefits and challenges (Table 4). Nonetheless, a recurring theme of these healthy diets is the consumption of unprocessed, whole, plant-based foods, with a growing body of literature showing the potential benefits for patients with CKD. Patients should be provided with the knowledge and resources to follow the best diet for their context and disease stage, and should be encouraged in that direction with the hope of improving their health to the extent possible. An essential part of supporting patients through any dietary change is referral to a (renal) dietitian who has an understanding of the risks and benefits of different dietary patterns. Future research should be focused on expanding the quality of evidence, including the number and size of RCTs. We strongly believe that a healthy diet has the potential to treat existing complications and to prevent the development of new ones, which is a win for patients, providers, and society.

Article Information

Authors' Full Names and Academic Degrees: Shivam Joshi, MD, Kamyar Kalantar-Zadeh, MD, MPH, PhD, Philippe Chauveau, MD, and Juan Jesus Carrero, PharmPhD.

Authors' Affiliations: Department of Medicine, Grossman School of Medicine, New York University, New York, New York (SJ); Department of Medicine, NYC Health + Hospitals/Bellevue, New York, New York (SJ); University of California–Irvine, Orange, California (KK-Z); Maison du Rein-Aurad Aquitaine, Gradignan, France (PC); Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden (JJC).

Address for Correspondence: Shivam Joshi, MD, Department of Medicine, NYU School of Medicine, 550 First Ave, New York, NY 10016. Email: shivam.joshi@nyulangone.org

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