Are low-carbohydrate diets safe in chronic or diabetic kidney disease?

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Abstract

Diabetes mellitus and obesity both contribute to chronic kidney disease (CKD) and diabetic kidney disease (DKD), and they can accelerate the loss of kidney function. Dietary intake can potentially have wide-reaching effects on the risk of CKD/DKD and their progression by reducing weight and blood pressure, improving glycemic control, reducing hyperfiltration, and modulating inflammation. Low-carbohydrate (LC) diets can reduce weight and improve glycemic control, but the high-protein content also raises concern in CKD/DKD. Empiric evidence supporting the kidney-related benefits or risks of LC diets is needed to understand the balance of these potential harms and benefits for patients with DKD and are the subject of our review.

Graphical abstract

Diabetes mellitus and obesity both contribute to chronic kidney disease (CKD) and diabetic kidney disease (DKD), and they can accelerate the loss of kidney function. Low-carbohydrate (LC) diets can reduce weight and improve glycemic control, but the high-protein content also raises concern in CKD/DKD. Empiric evidence supporting the kidney-related benefits or risks of LC diets is needed to understand the balance of these potential harms and benefits for patients with DKD and are the subject of our review.

Keywords

low-carbohydrate diets; chronic kidney disease; diabetic kidney disease

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Competing interests

The authors declare no competing interests.

Introduction

Diabetes mellitus and obesity both contribute to chronic kidney disease (CKD) and can accelerate the loss of kidney function. Diabetic kidney disease (DKD) results from a variety of mechanisms including kidney injury from advanced glycation end products, reactive oxygen species, inflammation, and glomerular hyperfiltration.¹ Obesity may also promote CKD by stimulating hyperfiltration directly or by causing metabolic syndrome and diabetes.² Dietary intake is a key component of prevention and management in both diabetes and obesity but may need to be tailored in patients with CKD.

Dietary intake can potentially have wide-reaching effects on the risk of CKD and CKD progression by reducing weight and blood pressure, improving glycemic control, reducing hyperfiltration, and modulating inflammation.^{3,4} Therefore, weight loss diets are attractive for patients either with or at risk for developing CKD. However, there are many unanswered questions about ideal macro- and micronutrient composition, macronutrient sources and dietary patterns in the management of DKD.⁵

Low-carbohydrate (LC) diets can reduce weight and improve glycemic control, but the higher protein content that often accompanies them also raises concern in CKD and DKD. On one hand, because both obesity and diabetes can contribute to a decline in kidney function, successfully treating these conditions with LC diets could improve or maintain kidney function (Fig. 1). On the other hand, the high-protein content of LC diets may promote hyperfiltration in the kidney, a risk factor for eventual kidney function decline.² Empiric evidence supporting the kidney-related benefits or risks of LC diets is needed to understand the balance of these potential harms and benefits for patients with DKD and will be the subject of our review.

There is no agreed upon definition for LC diets, and studies can be difficult to compare because they often recommend or report carbohydrate intakes at varying levels and in different units, such as g/day or percentage of energy consumption. For example, an early systematic review about the safety and efficacy of LC diets defined “lower-carbohydrate diets” and the “lowest-carbohydrate diets” as those with 60 and 20 g of carbohydrates daily, respectively.⁶ One study that compared a “low-carbohydrate, ketogenic diet” with a low-fat diet also stated that ketonuria occurs when carbohydrate consumption is less than 40 g daily.⁷ One recent meta-analysis defined LC diets as <45% of calories from carbohydrates⁸ and another used definitions that included <200 g/day of carbohydrates or 40% calories from carbohydrates.⁹

When carbohydrate intake is low enough, the body turns to other sources for energy. One key source of energy comes from metabolizing fat into ketones, otherwise known as ketogenesis. This process occurs in other instances such as very low-calorie intake, starvation, alcoholism, and notably, diabetic ketoacidosis, which occurs in people with type 1 diabetes mellitus (T1DM). Diabetic ketoacidosis, which is a medical emergency, occurs when patients with T1DM do not have insulin to halt the snowballing process of ketogenesis. However, in LC diets, ketosis can actually be a targeted goal because it signifies fat metabolism. Ketones can be detected in the blood, breath, and urine. Although detectable

ketones are not necessary for weight loss, for people trying to lower carbohydrate intake in order to achieve nutritional ketosis, restricting carbohydrate intake to <40 g daily may be necessary. In terms of dietary composition, lower daily levels of carbohydrate intake mean that intake of the other macronutrients—protein and/or fat—increases. Therefore, LC diets can be modestly higher in protein than typical diets, although fat intake is increased more substantially than protein intake.

Protein recommendations for CKD compared to western, LC, and post-bariatric surgery diets

Dietary recommendations for protein intake can vary based on age, gender, health, and weight management. For example, the U.S. Departments of Health and Human Services and Agriculture Dietary Guidelines for Americans recommends protein intake based on daily caloric intake, which varies with age and gender. The recommendations for adults with intakes of 1000, 2000, and 3000 kcal/day are 57, 156, and 198 g of protein, respectively. Based on the National Health and Nutrition Examination Survey data, the typical diet in the United States is approximately 59–72 and 73–109 g protein daily for women and men, respectively, and more than 90% of women and men met the recommendations.¹⁰ However, the recommendation can change in disease states, including CKD, and in treatment guidelines for post-bariatric surgery patients. The Endocrine Society recommends that post-bariatric surgery patients eat 60–120 g of protein/day to avoid protein malnutrition (serum albumin <3.5 mg/dL) and maintain muscle mass during their weight loss.¹¹

Most LC/HP diets vary by the amount of carbohydrates recommended, and the concomitant increase in protein is incidental, not prescribed. However, one review that examined the relationship between dietary protein and renal function defined a high-protein diet as one that included 1.5 g/kg of protein daily.¹² Based on dietary analysis from studies of LC diets, protein intakes have ranged between 73 and 130 g daily, which calculates to a range of 0.6–1.4 g/kg.^{7,13–15}

Chronic kidney disease

The Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease defines CKD as “abnormalities of kidney structure or function, present for >3 months, with implications for health.”¹⁷ Abnormalities of kidney function are generally measured by glomerular filtration rate (GFR) and albuminuria (see Tables 2 and 3). GFR is classified as G1 (>90, normal/high); G2 (60–89, mildly decreased); G3a (45–59, mildly to moderately decreased); G3b (30–44, moderately to severely decreased); G4 (15–29, severely decreased); or G5 (<15, kidney failure). Albuminuria can be classified as an albumin to creatinine ratio (mg/g): A1 (<30, normal to mildly increased); A2 (30–300, moderately increased); and A3 (>300, severely increased). The severity of CKD is classified primarily by a combination of GFR and the level of albumin excretion in the urine, which may reflect injury to the glomerular barrier. Both abnormally elevated and reduced GFR and a higher albumin or protein excretion, typically quantified by the urine albumin to creatinine ratio (UACR), are associated with worse kidney outcomes.

Diabetes is the most common cause of kidney disease (KD) in the United States.¹⁸ DKD may best be prevented or slowed by maintaining optimal glycemic control, controlling blood pressure, maintaining hydration, minimizing use of certain medications (e.g., nonsteroidal anti-inflammatory drugs) and using angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs) to lower glomerular hyperfiltration and reduce albuminuria.¹⁹

Guideline-based diabetes management

The American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology Diabetes Management Algorithm starts with lifestyle therapy—medical nutrition therapy, physical activity, adequate sleep, behavioral support, and tobacco cessation—and weight loss for patients who are overweight or obese.²⁰ The medical nutrition therapy these groups recommend includes a plant-based diet that is high in unsaturated and low in saturated and trans fats (Box 1).

The American Diabetes Association (ADA) recommends similar elements of lifestyle therapy, including weight loss for patients who are overweight or obese.²¹ In terms of medical nutrition therapy, the ADA acknowledges that the Mediterranean, dietary approaches to stop hypertension (DASH), and plant-based diets help manage diabetes in research studies. The ADA acknowledges that LC diets can also help manage diabetes but suggests they may only be appropriate for shorter durations (3–4 months) citing a lack of long-term research demonstrating benefit or harm. The ADA cites high-level evidence, however, to emphasize whole food sources of carbohydrate, and recommends minimizing the intake of refined carbohydrates and added sugars. For meal planning, the ADA recommends the diabetes plate method, which limits carbohydrates to 25% of the plate and recommends low-carbohydrate vegetables. The ADA also recommends reducing the consumption of refined carbohydrates and “strongly discourages” sugar-sweetened beverages, refined grains, and added sugars.

Obesity and CKD

While obesity may promote CKD through hypertension and type 2 diabetes mellitus (T2DM), it may also contribute to CKD by stimulating renal hyperfiltration, glomerular hypertrophy, and systemic inflammation (see Fig. 2).^{22–27} Multiple studies implicate obesity as an independent risk factor for declining GFR, proteinuria, and ESRD.^{28–32} In addition, proteinuria and GFR improve with weight loss.³³ Therefore, managing obesity could help prevent or manage CKD.

Guideline-based obesity management

The 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults recommends a BMI/comorbidity-based model to treat overweight and obesity, of which diabetes and hypertension are both comorbidities.³⁴ It recommends diets that create a 500–750-calorie or 30% energy deficit to achieve weight loss, and lists 15 dietary approaches proven to achieve weight loss, including LC diets. It also recommends pharmacotherapy and

bariatric surgery for patients with higher BMI levels and comorbidities. Similarly, the AACE recommends a “complication-centric model” to treat overweight and obesity, of which diabetes is a severe complication, so it warrants aggressive treatment with the intense lifestyle modification, pharmacotherapy, and bariatric surgery in a stepwise fashion.³⁵ The ADA also recognizes that weight management is an important part of diabetes management and acknowledges that intensive weight management programs vary in the types of food they restrict or emphasize.²¹

Dietary intake and CKD

The typical American diet is high in calories, both saturated and trans fats, fructose, carbohydrates, red meat, and sodium; whereas it is low in mono- and polyunsaturated fatty acids, plant-based protein, and fiber.³⁶ It has been implicated in KD because it is associated with obesity, hyperlipidemia, hyperuricemia, oxidative stress, inflammation, hypertension, and other CKD risk factors like metabolic acidosis and higher circulating phosphorus.^{36,37} Observational studies support beneficial associations between healthful patterns, such as the Mediterranean diet, the DASH diet, and other prudent dietary patterns with a lower risk of CKD,^{38–44} CKD progression, or mortality in patients with CKD.^{45,46}

Weight loss and CKD

Three comprehensive reviews of weight loss in CKD were published in 2009, 2012, and 2013.^{26,47,48} Overall these reviews concluded that individuals with significant weight loss usually have improved or stable GFR and levels of proteinuria in interventional and observational studies. The reviews included studies of lifestyle, pharmacological, and surgical interventions, and noted that both weight loss and CKD markers were usually better with surgical intervention, which leads to a greater weight loss, as compared with pharmacological and lifestyle interventions. However, none of the three analyses specifically quantified the relationship between the amount of weight lost and the level of improvement in GFR or proteinuria. Conclusions are limited because the duration of follow-up of the studies included ranged from 4 weeks for the interventional studies to several years for the observational cohort studies, several studies included less than 30 participants, and the measurements of renal function varied among studies. Therefore, long-term interventions are needed to see if there are improvements in hard clinical endpoints like sustained GFR or ESRD.

Lifestyle interventions

A secondary analysis of the Look AHEAD (the Action for Health in Diabetes) trial was published in 2014. It compared how diabetes support and education (DSE) and intensive lifestyle intervention (ILI) affected the development of “very-high-risk” CKD defined four ways: $\text{GFR} < 30 \text{ mL/min/1.73 m}^2$; $\text{GFR} < 45 \text{ mL/min/1.73 m}^2$ and $\text{UACR} > 30 \text{ mg/g}$; $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$ and $\text{UACR} > 300 \text{ mg/g}$; or renal replacement therapy. At 1 year, weight change in the DSE group was 0.7% versus 8.6% in the ILI group; and at the end of the study, the weight loss was 4 kg higher in the ILI group. Compared with those in the DSE group, those in the ILI group were 37% less likely to develop “very-high-risk” CKD.⁴⁹

Bariatric surgery

In 2016, a combined systematic review and meta-analysis examined the effects of bariatric surgery on renal function including ~30 studies. Although RCTs were sought, none were found. Included studies were categorized as one of the following terms: retrospective; nonrandomized, controlled retrospective; prospective; prospective cohort; prospective observational; observational prospective; prospective case-control; cohort; pilot; and case-control. All studies evaluated some measure of renal dysfunction—reduced GFR (<90 mL/min, not indexed for body surface area), glomerular hyperfiltration (GFR > 125 mL/min, not indexed for body surface area), or evidence of pathologic proteinuria (UACR >30 mg/g or total proteinuria >0.15 g/day) over a span of at least 4 weeks pre- and post-bariatric surgery. Overall, hyperfiltration was measured in six studies, and its risk was reduced by 54%. Albuminuria or total proteinuria was measured in 16 studies, and their risk was reduced by about 60% to 70%.⁵⁰ A series of cohort studies published after this review also reported the benefits of bariatric surgery in terms of either improved creatinine and GFR or decreased incidence of stage 4/ESRD.^{51–55}

The greater improvement in renal parameters observed with surgical interventions may have been due to the greater associated weight loss and not an intrinsic effect of surgery. Bariatric surgery has a greater initial and sustained weight loss than lifestyle interventions.⁵⁶ Because bariatric surgery effectively promotes weight loss, it could be an effective treatment for DKD.⁵⁷

Weight loss and DKD

In 2015, a narrative review on weight loss and DKD was published.⁵⁸ It included 26 studies—16 using bariatric surgery, 8 using lifestyle modification, and 2 using pharmacologic therapies—of individuals with obesity, diabetes, and DKD. Similar to the reviews of weight loss and CKD, this review found that weight loss was associated with decreases in proteinuria and increases in GFR. Additionally, more weight loss and better improvements were associated with bariatric surgery.

An RCT published in 2013 was not included in the previous review.⁵⁹ In this 12-month study, 45 participants with T2DM and renal disease completed either a standard protein diet (n = 24) or a moderate protein diet (n = 21) for weight loss. The goal nutrient composition in the moderate protein diet was 30% protein (90–120 g protein/day), 30% fat, and 40% carbohydrate. The goal nutrient composition in the standard protein diet was 20% protein (55–70 g protein/day), 30% fat, and 50% carbohydrate. Weight loss was not significantly different between groups: 9.7±13.4 kg and 6.6±7.1 kg in the moderate and standard protein diets, respectively. GFR was measured by iothalamate and did not change significantly over the course of the study for either group. However, when participants were analyzed by baseline CKD stage regardless of diet intervention, the GFR of those in stages 1, 2, and 3 (n = 33) increased by 4 mL/min and the GFR of those with hyperfiltration (n = 12) decreased by 15 mL/min.

A small study published in 2013 placed six patients with obesity, diabetes, and diabetic nephropathy (GFR < 40 mL/min/1.73 m² and UACR > 30 mg/day) on an 800 kcal/day diet

with 75 g of protein and less than 50 g of carbohydrates daily to stimulate ketosis. In the second week of the 12-week intervention, participants were encouraged to exercise and expend 2000 calories per week.⁶⁰ All patients were using ACEIs or ARBs. The median (min, max) weight for the group at baseline and 12 weeks was 118.5 kg (94.8, 140.0) and 104.3 kg (85.0, 115.8), respectively. Compared with baseline, at 12 weeks, serum creatinine decreased by 12%. Although there were significant reductions in weight and serum creatinine, the reduction in albuminuria was not significant. This may have been due to the small sample size.

LC diets and T2DM

A network meta-analysis published in 2018 examined the comparative efficacy of nine dietary approaches in 56 trials at controlling hemoglobin A1c (HA1c) and fasting glucose in patients with T2DM.⁶¹ The dietary approaches included low-carbohydrate (<25% total energy consumption (TEC) as carbohydrate); Mediterranean; Paleolithic; vegetarian; low glycemic index/load; moderate carbohydrate (25–45% TEC as carbohydrate, 10–20% TEC as protein); high protein (>20% TEC as protein, <35% TEC as fat); low-fat (<30% TEC as fat); high intake of cereals and grains; 10–15% TEC as protein); and control (no or minimal intervention). In this analysis, while all the diets lowered HA1c (range: 0.47–0.82%) and fasting glucose (range: 1.00–1.61 mmol/L), the LC diet was ranked the best at lowering HA1C and second best (after Mediterranean diet) at lowering fasting glucose. However, the analysis did not include renal outcomes.

Renal concerns about LC Diets

Concerns about kidney function on LC diets refer primarily to the high protein content as opposed to the low level of carbohydrate intake (see Fig. 3). Multiple human physiologic studies have demonstrated renal hyperfiltration in response to high protein consumption as a direct physiologic effect.^{2,62,63} Compared with plant and milk protein, these effects are greater with animal proteins^{12,64,65}—the foundation of most LC diets.⁶⁶ Although the exact causes for this phenomenon are not fully understood, effects related to a specific amino acid composition and dietary advanced glycation end products have been proposed.^{67,68} Renal hyperfiltration, however, is an adaptation to both physiologic and disease stimuli, and it is not clear whether it always represents a risk factor for progressive CKD.²

LC diets may additionally increase the risk for kidney stone formation because they can increase urinary calcium and uric acid, and lower urinary citrate and pH.^{66,69,70}

Unfortunately, many trials of LC diets versus other diets have not systematically reported adverse events, and we could not find any such reporting in systematic reviews. To our knowledge, kidney stone events have been infrequently reported in patients following LC diets.

Protein intake and kidney function

The Modification of Diet in Renal Disease (MDRD) studies influenced the recommendations regarding protein intake in nondiabetic CKD. The goal of the studies was to determine whether lower protein intake slows the decline of renal function. Study A

included 585 individuals with GFR between 25 and 55 mL/min/1.73 m² who were randomized to either a usual (1.3 g/kg/day) or a low protein (0.58 g/kg/day) diet. Study B included 255 patients with GFR between 13 and 24 mL/min/1.73 m² who were randomized to either a low (0.58 g/kg/day) or a very low protein (0.28 g/kg/day) with a ketoacid amino supplement.⁷¹ Neither study A nor study B showed a benefit for either a low or very low-protein diet to slow the decline of renal function for an average of 2.2 years of follow-up. A secondary as-treated analysis of the MDRD data showed that a reduction of protein intake may have slowed the decline of GFR by as much as 29% per 0.2g protein/kg/day reduction.⁷² Additional secondary analyses suggest a potential benefit on the rate of eGFR decline if the acute effects of protein intake on GFR were ignored.⁷³ These are, however, post hoc analyses and cannot be viewed as definitive. At over 6 years of follow-up, the participants on the very low-protein diet in study 2 had a higher incidence of death and malnutrition as measured by serum albumin.⁷⁴ Based on this study and other meta-analyses, KDIGO suggests that individuals with stages G4 and G5 CKD consume ~0.8 g/kg of protein daily rather than lower levels. Based on the average weight in the U.S. population, this would correspond with 61 and 71 g protein daily for women and men, respectively.

A systematic review and meta-analysis published in 2014 included 30 studies, and it compared the kidney function of individuals without CKD on high- versus low-protein/normal diets.⁶⁶ The thirty studies included were either RCTs or crossover designs. Studies were excluded if they included participants with GFR < 60 mL/min/1.73 m², T1DM, or macroalbuminuria. Study duration ranged from 1 week to 24 months. Protein content was expressed in multiple ways: % total energy consumption (TEC), g/kg body weight (BW)/day, LC diet, or very low-carbohydrate diet (VLCD). High-protein diets ranged from 20 to 40% TEC; 1–2.4 g/kg BW/day; LCD; or VLCD. Low-protein/normal diets ranged from 10 to 20% TEC or 0.6–1.3 g/kg BW/day. This study found that mean difference in GFR was higher on high-protein diets by 7.18 mL/min/1.73 m² (95% CI 4.45–9.91).

One analysis of the Atherosclerosis Risk in Community (ARIC) study that was published in 2017 showed that compared with those in the lowest quintile for consumption of red and processed meat, individuals in the highest quintile of red and processed meat were 23% more likely to develop CKD. However, compared with individuals in the lowest quintile for legume, nut, and low-fat dairy consumption, those in the highest quintiles were 17%, 19%, and 25% less likely to develop CKD, respectively.⁷⁵

These results are similar to those found in the Nurses' Health Study (NHS) analysis that was published in 2003.⁶⁵ For individuals with normal kidney function (GFR > 80 mL/min/1.73 m²), protein intake was not associated with the change in renal function over 11 years, and there was no difference in kidney function decline between the lowest and highest quintile of protein consumption. However, for those with mild renal insufficiency (GFR between 55 and 80 mL/min/1.73 m²), GFR declined by 7.72 mL/min/1.73 m² per 10 g higher protein intake.⁶⁵ In some models, non-dairy animal protein, but not dairy and vegetable protein, was particularly associated with a decline in GFR.

Protein intake and DKD

In 2013, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial examined the association between diet and the incidence or progression of CKD in individuals with T2DM.⁴² The combined renal outcome of incident or progression of CKD was defined as new microalbuminuria, new macroalbuminuria, GFR decline >5% per year, and ESRD. Compared with individuals in the lowest tertile of protein consumption, those in the highest tertile were 14% *less* likely to experience incident or progression of CKD. Compared with individuals in the lowest tertile for carbohydrate consumption, those in the highest tertile were 15% *more* likely to experience incident or progression of CKD.

Results from the ONTARGET trial, among individuals with DKD, differ from the ARIC and NHS, where participants had CKD, but not necessarily diabetes. It is also important to recognize that ARIC, NHS, and ONTARGET studies are observational in design, so causation cannot be determined.

A meta-analysis published in 1996 examined the effect of dietary protein restriction on renal disease.⁷⁶ The analysis for diabetic renal disease included five studies—three were RCTs and two had a nonrandomized crossover design. Compared with individuals with diabetic renal disease following a usual protein diet, those whose protein was restricted to 0.5–0.85 mg/kg body weight were 44% less likely to develop worsening kidney function (decline in GFR or creatinine clearance or increase in albumin excretion). Although this analysis described changes in blood pressure and HA1C, it described no weight change that may have been associated with the protein restriction. Additionally, this study occurred before the widespread use of ACE inhibitors and ARBs and did not assess for evidence of malnutrition from protein restriction.

A more recent meta-analysis from 2008 examined the effects of lowering protein intake on diabetic nephropathy in patients with T1DM or T2DM.⁷⁷ This analysis included eight RCTs. There was no significant difference in the change in GFR between the normal and low-protein (0.6–0.8 g protein/kg body weight) diet groups. However, compared with those in the normal protein group, individuals in the low-protein diet group had lower HA1C, less proteinuria, and lower serum albumin. This analysis also did not describe any weight change that might have occurred during the studies. The authors expressed the concern that the lower serum albumin that occurred in patients on the lower protein diet might lead to malnutrition. The authors also noted that lower proteinuria was associated with lower serum albumin.

The outcomes of these two meta-analyses may be different because of differences in their inclusion criteria. The earlier analysis included studies with a crossover design, and the later analysis specifically excluded crossover studies because of “carryover effects and the tendency of diabetic nephropathy to progress quickly.”⁷⁷

A Cochrane review examining the effects of protein intake on DKD progression was published in 2007.⁷⁸ It included nine RCTs and three pre-/post-design trials of individuals with T1DM or T2DM randomized to reduced or modified protein diets that lasted for at least

4 months, and the duration of the studies lasted from 4.5 months to 4 years. The primary outcomes were all-cause mortality, ESRD, and GFR. The amount of protein in the low-protein and control diets were 0.3–0.8 g/kg/day varied from 1 to 2 g/kg/day, respectively. Two studies tested a vegetarian, low-protein diet. Only one study included mortality and ESRD, and it found that those on a low-protein diet were 77% less likely to experience those endpoints. However, the authors concluded there was a nonsignificant decrease in the progression of DKD for individuals on protein-restricted diets. The authors noted that individuals find it difficult to adhere to protein-restricted diets and that such diets would delay dialysis by only one or two months. In addition, the authors noted that malnutrition was a potential adverse effect of low-protein diets.

LC diets in normal kidney function

Although most studies of LC diets have excluded patients with CKD, many studies of LC diets report renal outcomes in their patient samples that have normal kidney function. A meta-analysis published in 2016 examined how LC diets (defined as <45% of calories from carbohydrate) affected renal function in individuals without CKD, which was defined as $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$.⁸ The primary outcome was the mean change in eGFR. One study used creatinine clearance, which the authors considered the same as eGFR. Two studies used serum creatinine to calculate eGFR. The analysis included nine randomized controlled trials, four of which included patients with diabetes. The duration of the studies ranged from 6 to 24 months. The studies included between 12 and 144 individuals. The definition of an LC diet varied from 4 to 40% TEC or 14 to 130 g/day. The protein content of the LC diets ranged from 30% to “no restriction” or <110–124 g/day. The protein content of the control diet ranged from 15% to “no restriction” or <65–85 g/day or 1.0–1.2 g/kg BW/day. The authors only included participants who completed the studies—452 in the LC diet group and 520 in the control group. The change in eGFR for those on the control diet ranged from -4.1 to $10.8 \text{ mL/min/1.73 m}^2$. The change in eGFR for those on the LC diets ranged from -4.7 to $24.0 \text{ mL/min/1.73 m}^2$. The authors concluded that compared with control diets, LC diets increased GFR by $0.13 \text{ mL/min/1.73 m}^2$ (95% CI 0.00–0.26). The authors postulated that the difference might be a consequence of the higher protein content in the LC diet, but also noted that it may not be clinically significant.

LC diets in renal function with diabetes

A meta-analysis published in 2018 examined how LC diets affected renal function in patients with T2DM.⁹ Although the analysis included 12 randomized controlled trials, not all outcomes were available for all trials. Outcomes of kidney function included were eGFR (four trials), creatinine clearance (five trials), urinary albumin excretion (three trials), serum creatinine (nine trials), and serum uric acid (three trials). The definition of an LC diet varied from <200 g/day of carbohydrate or <40% calories from carbohydrates. The protein content in the LC diet ranged from 27% to 30% (not provided in three studies). The protein content in the control diet ranged from 15% to 20% (not provided in one study). The duration of the studies ranged from 5 weeks to 24 months. The authors reported the standard mean difference (SMD) between the LC and control diets: eGFR 0.26 (−0.03, 0.55); creatinine clearance 0.51 (−0.38, 1.40); urinary albumin excretion −0.04 (−0.75, 0.67); serum

creatinine -0.57 ($-1.51, 0.38$); and serum uric acid -0.86 ($-4.00, 2.28$). The authors concluded that the LC diet did not have any beneficial or detrimental effect on the kidney function of individuals with T2DM although they noted that longer-term studies are needed. However, there was no indication of baseline renal dysfunction among participants.

Conclusions

Obesity and diabetes contribute to CKD/DKD by several mechanisms, including advanced glycation end products, reactive oxygen species, inflammation, and glomerular hyperfiltration.¹ Weight loss, such as treating obesity, improves both diabetes and CKD/DKD. LC diets can treat both obesity and diabetes, but they are discouraged in CKD/DKD because of concerns that the relatively high protein content of LC diets will accelerate renal function decline. However, the data for protein consumption leading to renal function decline in CKD are inconclusive.

Most of the evidence about LC diets and renal function is in individuals with normal kidney function, even in those with diabetes. However, there is some evidence that individuals with CKD who undergo bariatric surgery have improved renal function, and the diet recommended post-bariatric surgery is relatively high in protein. Since bariatric surgery results in more substantial weight loss, the amount of weight loss may overshadow any potential negative effects of a high-protein diet on kidney function, resulting in confounding.

Because of the observed weight loss and cardiometabolic benefits of LC diets, patients with CKD and DKD may choose to follow or be recommended such a nutritional approach. Given that lowering carbohydrate intake can profoundly lower glycemia and lead to diuresis, hypoglycemic medications need to be adjusted by an experienced clinician, and hydration and electrolyte intake should be emphasized. Further, since the LC diet effects on kidney function remain uncertain, more frequent monitoring is warranted in patients with CKD.

To adequately address the question of whether LC diets can be safely used in individuals with CKD and DKD, we need prospective RCTs with individuals with CKD/DKD and measured baseline GFR and proteinuria. To determine diet adherence, the macronutrient content of LC diets actually consumed needs to be measured carefully. Primary outcomes should include measured GFR and proteinuria, time to ESRD or transplant, and ideally, survival, primarily because this outcome has not been measured in an RCT of an LC diet intervention. Secondary outcomes should include dietary adherence, weight, body composition, HbA1c, blood pressure, lipids, medications, and quality of life. Such an RCT would greatly inform the decades-long debate about the use of LC diet interventions in people with CKD and/or DKD.

Acknowledgments

N.S.M. was funded, in part, by the National Institutes of Health Grant K01HL115599. J.J.S. was funded, in part, by the National Institutes of Health Grant R01DK111952.

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Box 1.

AACE/ACE guideline recommendations for treatment of diabetes Lifestyle modification.

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(+) Promotes outcome.

(-) Inhibits outcome.

(?) Unknown relationship to outcome.

Figure 1.

Diagram of the relationship between obesity, diabetes, CKD, and LC diets.

Figure 2.
Proposed mechanisms for the effect of obesity on renal function.

Figure 3.
Theoretical concerns about increased protein intake and kidney function.

Table 1.

Protein content in different diets

Diet	Daily protein (g)
Western diet	Women: 59–72
	Men: 73–109 ^a
KDIGO recommendation:	
Stages G1–3	Women: 61–107
	Men: 71–124 ^b
Stages G4/5	Women: 46–61
	Men: 53–71 ^b
LC diet	73–130
Post-bariatric surgery diet	60–120 ¹¹

^aBased on NHANES.¹⁰

^bBased on average weight of women and men in the United States.¹⁶

Abbreviations: LC diet, low-calorie diet; KDIGO, the Kidney Disease: Improving Global Outcomes; NHANES, the National Health and Nutrition Examination Survey.

Table 2.

Chronic kidney disease stages classified by glomerular filtration rate

CKD stage	GFR (ml/min/1.73m ²)	Qualitative category
Stage 1	G1: ≥90	Normal/high
Stage 2	G2: 60–89	Mildly decreased
Stage 3a	G3a: 45–59	Mildly to moderately decreased
Stage 3b	G3b: 30–44	Moderately to severely decreased
Stage 4	G4: 15–29	Severely decreased
Stage 5	G5: <15	Kidney failure/end-stage renal disease

Table 3.

Chronic kidney disease classified by albuminuria

Albumin-to-creatinine ratio (mg/g)	Qualitative category
A1: <30	Normal to mildly increased
A2: 30 – 300	Moderately increased
A3: >300	Severely increased