Retrospective cohort study of changes in estimated glomerular filtration rate for patients prescribed a low carb diet

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Purpose of review
Obesity and diabetes contribute to chronic kidney disease (CKD) and accelerate the loss of kidney function. Low carbohydrate diets (LCDs) are associated with weight loss and improved diabetes control. Compared to the typical Western diet, LCDs contain more protein, so individuals with CKD are not included in studies of LCDs. Therefore, there are no studies of LCDs for weight loss and their effects on kidney function.

Recent findings
Obesity, hyperglycemia, and hyperinsulinemia can be detrimental to kidney function. LCDs may improve kidney function in patients with obesity and diabetes because they are associated with weight loss, improve blood sugar control, and decrease endogenous insulin production and exogenous insulin requirements.

Summary
In this study, for patients with mildly reduced and moderately to severely reduced kidney function who were prescribed an LCD, their estimated glomerular filtration rate (eGFR) was either unchanged or improved. For those with normal or elevated eGFR, their kidney function was slightly decreased. For those without diabetes, greater weight loss was associated with improved eGFR. Future studies should prospectively measure low carbohydrate dietary adherence and physical activity and directly measure changes in GFR and albuminuria for participants with CKD before and during that diet.

Keywords
chronic kidney disease, low carbohydrate diets, obesity, weight loss

INTRODUCTION

Because diabetes and obesity contribute to chronic kidney disease (CKD) and accelerate the loss of kidney function, successfully treating these conditions may prevent and slow the progression of CKD. Weight loss is usually the primary goal of obesity treatment, but it is also one of the most potent therapies for diabetes [1]. Weight loss of 5% or more is considered clinically significant because it improves weight-related comorbidities, including diabetes and CKD [2–5]. In some studies, compared to low-fat diets, low carbohydrate (LCDs) have led to more weight loss; better diabetes control; lower triglycerides; and higher high-density lipoprotein (HDL) cholesterol levels [6,7]. However, individuals with CKD were not typically included in studies of LCDs. Consequently, even though LCDs can treat both obesity and diabetes, the kidney-related effects of LCDs in CKD are still unknown [8].

Concerns about LCDs in CKD exist because compared to a standard diet, they contain higher protein. Higher protein consumption may promote renal hyperfiltration, a risk factor for eventual kidney function decline [9]. Additionally, compared to

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KEY POINTS

- Obesity and diabetes contribute to chronic kidney disease and accelerate the loss of kidney function.
- Low carbohydrate diets may improve kidney function in patients with obesity and diabetes because they are associated with weight loss, improve blood sugar control, and decrease insulin requirements.
- Future studies should prospectively measure low carbohydrate dietary adherence and directly measure changes in GFR and albuminuria for participants with chronic kidney disease before and during that diet.

patients with CKD who consume protein from plant sources, those who consume protein from animal sources, such as meat, eggs, and cheese, have an increased risk for developing several metabolic abnormalities. These include (1) chronic metabolic acidosis, which contributes to muscle wasting [10], bone loss [11], and kidney function decline [12], which may require treatment with alkali therapy; (2) uremia, which may require a reduction in dietary protein; and (3) increased urinary calcium and uric acid with lower urinary citrate and pH, which may lead to kidney stones even in normal kidney function [13,14] and may require therapeutic intervention.

LCDs may improve kidney function in patients with obesity and diabetes because of their effects on hyperinsulinemia. Hyperinsulinemia is caused by insulin resistance, can be associated with excess weight, and can damage kidney function in multiple ways, including insulin-related increases in renal angiotensin receptors and endothelin [15]. These changes can lead to elevated blood pressure. LCDs lower insulin levels because lower carbohydrate ingestion leads to decreased endogenous insulin production and requires lower doses of exogenous insulin. The objective of this study is to model the changes in estimated glomerular filtration rate (eGFR) in a cohort of patients in a clinic where an LCD is almost exclusively prescribed and explore associations with initial eGFR category.

METHODS

Study design

This is a retrospective cohort study of longitudinal change in kidney function of overweight and obese patients with at least two visits with an outpatient ketogenic diet provider from January 1, 2001, to February 25, 2020. The program was formally implemented with the advent of the Keto Medicine Clinic (née Lifestyle Medicine Clinic) in 2006. The data were retrieved from the electronic health record (EHR). The protocol was designated as expedited and approved by the Duke Institutional Review Board.

Study participants

Figure 1 is a diagram of study inclusion. Study participants were those with at least two visits with keto diet provider, aged $\geq$ 18 years, with a body mass index (BMI) $\geq$ 25 kg/m^2, with creatinine measurements in the baseline and Q4 periods (defined below). Because measures of albuminuria were not available for all individuals, we categorized kidney function using eGFR cutoffs defined by the KDIGO classification [16]. E1 (normal or high), E2 (mildly reduced), E3 (moderately to severely reduced), E4 (severely reduced), and E5 (kidney failure) were defined as eGFR $\geq$ 90, 60–89, 30–59, 15–29, and $<$ 15 ml/min/1.73 m^2, respectively [16]. Individuals were excluded from the analysis in the following order:

(1) Age $<$ 18 years
(2) BMI $<$ 25 kg/m^2
(3) eGFR $<$30 (post hoc)
(4) eGFR unknown (post hoc)

Description of the keto medicine clinic

Eric Westman, MD, MHS, operates the Keto Medicine Clinic at Duke University. Dr Westman prescribes a low carbohydrate, high fat, relatively high-protein diet to patients with overweight and obesity almost exclusively. Patients attend a group visit where the low carbohydrate diet is reviewed and they can ask questions. Patients are also given handouts with detailed instructions, including the recommendation to consume less than 20 g of carbohydrates daily to stay in a ketogenic state of weight loss. Patients are told they do not need to limit the amount of protein or fat they consume. At the patients' initial clinic visits, baseline labs may be drawn and diabetes medications may be reduced or discontinued. Depending on comorbidities, the recommended follow-up visits can vary from 1 to 4 weeks.

Measurement time points

Outcomes were measured during specific time periods. Enrollment was defined as the date of the first encounter in the Keto Medicine Clinic. Baseline measures were calculated during the 'pre-enrollment' quarter from 1 to 90 days prior to enrollment. Differences between median values in the baseline

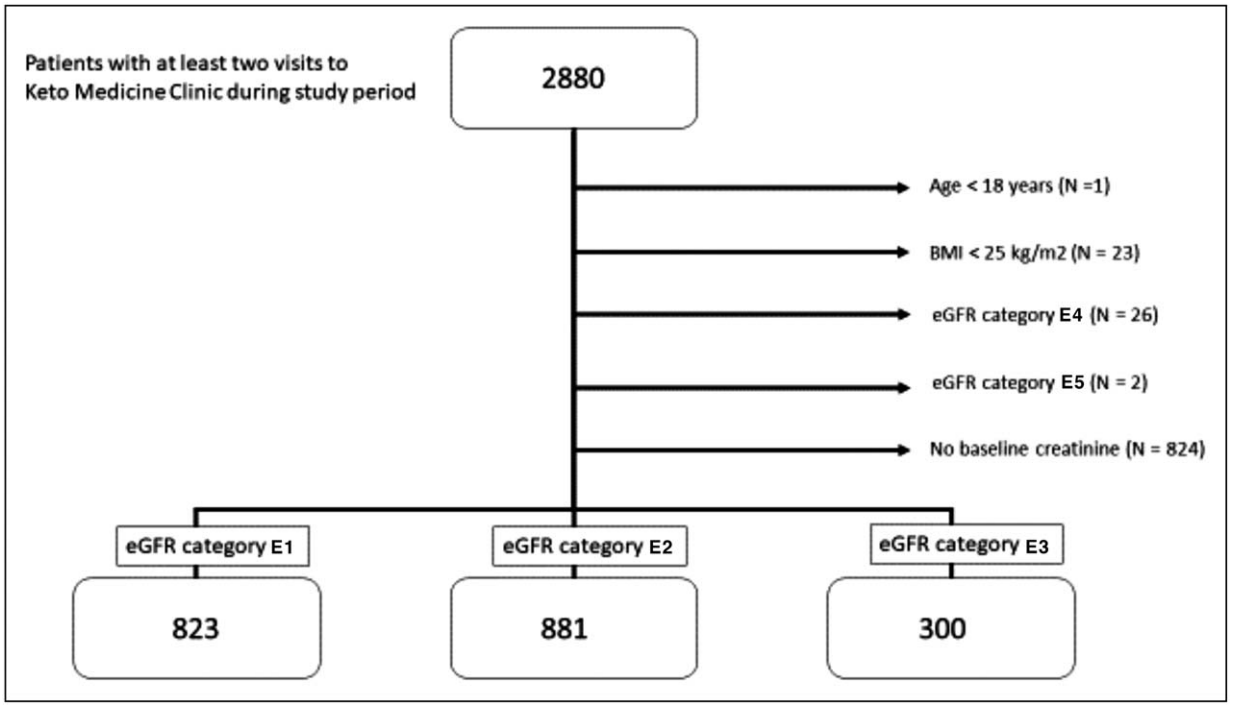

FIGURE 1. Study inclusion.

quarter and Q4 (270–365 days) following enrollment were calculated.

Measures

Extracted variables include weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), and serum total cholesterol, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), triglycerides (TGs), and creatinine. HDL and LDL values include those that were measured directly and calculated. Implausible values were removed based on rules defined by clinical authors (see Supplemental Table 1, http://links.lww.com/COE/A25). Laboratory outcomes with fewer than 100 values were not considered for inclusion. Lab variables with negative values were considered input errors and treated as missing data.

Weight, height, SBP, and DBP were obtained from the vital signs fields from all outpatient visits in the health system. Weight and height were used to calculate BMI. For BMI, height values were often missing, so we imputed the median of existing heights for weights without corresponding height values to calculate BMI for every weight value in the record.

Percentage weight change from baseline weight served as a proxy for diet adherence. Weight change was categorized in increments of 5 percent weight loss. Because it is not influenced by initial weight, percentage weight loss has advantages over other measures of weight change [17].

The eGFR was calculated from raw serum creatinine values using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [18]. For serum creatinine values greater than 10, eGFR was set to missing. The median calculated eGFR in the baseline period was used to report eGFR category prior to clinic enrollment.

Diagnoses of hypertension and diabetes were defined by International Classification of Diseases 9 and 10 codes associated with enrollment encounter. Medication usage was assumed if a medication was included in the medication list associated with any visit in the 90 days prior to the first encounter in the Keto Medicine Clinic.

Statistical analysis

Longitudinally assessed outcomes were analyzed as median quarterly values, baseline quarter vs. Q4.

Pre-enrollment characteristics were calculated for patients by pre-enrollment eGFR category as mean ± standard deviation or median with interquartile range for continuous variables and percentages for categorical variables. A category for 'unknown' is presented to describe potential patterns of bias due to nonrandom missingness.

Initial comparisons were unadjusted change in eGFR at one year by weight change status in Q4

following clinic enrollment over initial eGFR status. Three regression models were conducted to estimate eGFR change from baseline in Q4. Covariates in model 1, the first exploratory model, included percentage weight change in Q4, baseline eGFR category, and two-way interaction terms. Model 2, the second exploratory model, included all of the covariates in model 1 plus demographic characteristics (age, race, sex) and initial diabetes status. In model 2, diabetes status was included as a three-way interaction with GFR and percentage weight change. Model 3, the third exploratory model, included all terms from model 2 with additional adjustment for initial SBP and DBP. All linear models were evaluated for statistical assumptions using visual plots of residuals and statistics of leverage and influence. Sensitivity analyses were performed using robust regression for variables with heteroscedasticity due to the presence of outliers. Analyses were conducted using Stata/SE Version 16 (College Station, TX).

RESULTS

The initial cohort included 2,880 individuals. Almost two-thirds of the cohort were in eGFR category E1 or E2, 29% and 31%, respectively, and another 11% were in eGFR category E3. Very few individuals were in EGFR categories had either E4 or E5, 1% and <1%, respectively; therefore, they were not included in the final analysis. eGFR category was unknown for 29% of the cohort because they did not have a serum creatinine in the EHR for 90 days before their first visit to the Keto Medicine Clinic, so they were not included in the analysis either. Therefore, the final analysis included 2004 individuals. More than three-quarters of the final cohort were in either category E1 or E2, 41% and 44%, respectively, and another 15% were in category E3.

Table 1 shows the baseline characteristics for the 2004 patients included in the analysis by eGFR category, including medical conditions, medications, and baseline lab values. Mean (SD) is reported for variables with normal distributions and median (IQR) is reported for variables without normal distributions.

Medical conditions

Hypertension. Of the 1842 and 1833 individuals with SBPs and DBPs, respectively, the mean (SD) SBP and DBP were 132 (16) and 79 (9), respectively. Forty-five percent ($N = 905$) had a diagnosis of hypertension in the problem list. *Diabetes.* Only 29% ($N = 589$) of the cohort had a diagnosis of diabetes, but that included almost half of the individuals in the E3 group. *Dyslipidemia.* In terms of lipid panel components available at baseline, the numbers varied – LDL ($N = 1236$), HDL ($N = 1305$), and triglycerides ($N = 705$), with mean (SD) or median (IQR) of 107 (36), 46 (38, 55), and 127 (92, 190), respectively.

Medications

Hypertension. Twenty-three percent ($N = 466$) of the cohort was prescribed either an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker. *Diabetes.* Fifteen percent ($N = 303$) of the cohort was prescribed metformin; 1% ($N = 19$) were on pioglitazone; and 9% ($N = 177$) were on insulin, though 20% ($N = 58$) in the E3 group were prescribed insulin. Only 2% and 1% of the cohort were prescribed glucagon-like peptide 1 (GLP1) agonists and SGLT2 inhibitors, respectively. *Prednisone.* Six percent ($N = 111$) of the cohort was prescribed prednisone in the 90 days preceding their first visit to the Keto Medicine Clinic.

Table 2 shows the categorical weight change by eGFR category at the end of follow-up, 30% lost at least 5% of their initial weight; for patients with E3, this number was 38%. Weight measurements were not available for 38% of patients.

Figure 2 and supplemental Table 2, http://links.lww.com/COE/A26 depict the estimated change in eGFR by weight change, eGFR category, and diabetes status for model 2, which was adjusted for age, race, and sex. Panels A and B show those without and with a diagnosis of diabetes at enrollment, respectively. For those in the E1 category (in green), without and with diabetes, and across all weight change categories, the model predicts eGFR would decrease by approximately 4–6 ml/min/1.73 m^2.

For those in the E2 category (in red) without diabetes, the model predicts the eGFR would improve between 3 and 4 ml/min/1.73 m^2 for all weight change categories. For those in the E2 category with diabetes, the model predicts the eGFR would improve between 1 and 3 ml/min/1.73 m^2 for all weight change categories.

For those in the E3 category (in blue), without diabetes, and with 5% weight loss (i.e., adherent to the LCD), the eGFR would improve by about 3 ml/min/1.73 m^2; those with E3, without diabetes, and no weight change, the eGFR would improve by about 1 ml/min/1.73 m^2; and those with E3, without diabetes, and 5% weight gain, the eGFR would decline by 1 ml/min/1.73 m^2. For those in the E3 category with diabetes, the eGFR was essentially unchanged across all weight change categories.

However, it is important to note that the 95% confidence intervals (see Supplemental Table 2, http://links.lww.com/COE/A26) for the estimated change at each weight change category within the

Table 1. Baseline patient characteristics

Factor	Level	Total	E1	E2	E3
N		2004	823 (41%)	881 (44%)	300 (15%)
Age at First Visit, mean (SD)		53 (12)	48 (11)	56 (11)	62 (10)
Race	White	1014 (51%)	321 (39%)	522 (59%)	171 (57%)
	Black or African American	920 (46%)	467 (57%)	331 (38%)	122 (41%)
	Other	70 (3%)	35 (4%)	28 (3%)	7 (2%)
		N = 1834	*N* = 754	*N* = 798	*N* = 282
Weight (kg), median (IQR)		112 (96, 132)	114 (96, 135)	110 (96, 129)	112 (98, 129)
BMI, median (IQR)		40 (35, 47)	41 (35, 48)	39 (35, 46)	39 (35, 46)
		N = 2004	*N* = 823	*N* = 881	*N* = 300
eGFR, mean (SD)		84 (22)	106 (12)	76 (8)	49 (8)
		N = 1842	*N* = 758	*N* = 802	*N* = 282
SBP, median (IQR)		131 (122, 141)	130 (122, 140)	131 (122, 142)	132 (121, 142)
		N = 1833	*N* = 755	*N* = 800	*N* = 278
DBP, median (IQR)		79 (73, 85)	81 (75, 87)	79 (73, 85)	76 (69, 82)
		N = 708	*N* = 307	*N* = 306	*N* = 95
Tot Chol, median (IQR)		181 (153, 210)	177 (152, 206)	185 (157, 214)	176 (145, 208)
		N = 1236	*N* = 536	*N* = 545	*N* = 155
LDL, median (IQR)		105 (82, 130)	104 (84, 125)	108 (83, 135)	98 (73, 117)
		N = 1305	*N* = 565	*N* = 569	*N* = 171
HDL, median (IQR)		46 (38, 55)	45 (38, 55)	45 (37, 55)	46 (38, 54)
		N = 705	*N* = 306	*N* = 305	*N* = 94
Triglycerides, median (IQR)		127 (92, 190)	126 (87, 184)	126 (94, 193)	134 (102, 209)
Medical conditions					
Diabetes	No	1415 (71%)	619 (75%)	636 (72%)	160 (53%)
	Yes	589 (29%)	204 (25%)	245 (28%)	140 (47%)
Hypertension	No	1099 (55%)	487 (59%)	462 (52%)	150 (50%)
	Yes	905 (45%)	336 (41%)	419 (48%)	150 (50%)
Medications					
Pioglitazone	No	1973 (99%)	815 (99%)	867 (99%)	291 (99%)
	Yes	19 (1%)	6 (1%)	10 (1%)	3 (1%)
Insulin	No	1815 (91%)	768 (94%)	811 (92%)	236 (80%)
	Yes	177 (9%)	53 (6%)	66 (8%)	58 (20%)
Metformin	No	1689 (85%)	693 (84%)	743 (85%)	253 (86%)
	Yes	303 (15%)	128 (16%)	134 (15%)	41 (14%)
Prednisone	No	1881 (94%)	779 (95%)	828 (94%)	274 (93%)
	Yes	111 (6%)	42 (5%)	49 (6%)	20 (7%)
ACE Inhibitors	No	1687 (85%)	708 (86%)	736 (84%)	243 (83%)
	Yes	305 (15%)	113 (14%)	141 (16%)	51 (17%)
ARBs	No	1831 (92%)	772 (94%)	810 (92%)	249 (85%)
	Yes	161 (8%)	49 (6%)	67 (8%)	45 (15%)
SGLT2 Inhibitors	No	1979 (99%)	818 (100%)	870 (99%)	291 (99%)
	Yes	13 (1%)	3 (<1%)	7 (1%)	3 (1%)
GLP1 Agonists	No	1958 (98%)	810 (99%)	860 (98%)	288 (98%)
	Yes	34 (2%)	11 (1%)	17 (2%)	6 (2%)

ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; SGLT2, sodium glucose co-transporter 2; GLP1: glucagon-like peptide 1.

Table 2. Weight change category by eGFR category

Weight change category	All participants *N* (%)	E1*	E2*	E3
Total	**2004**	**823 *N* (%)**	**881 *N* (%)**	**300 *N* (%)**
≥ 10% weight loss	324 (16)	102 (12)	157 (18)	65 (22)
5 to <10% weight loss	283 (14)	105 (13)	129 (15)	49 (16)
0 to < 5% weight loss	338 (17)	151 (18)	138 (16)	49 (16)
Weight gain	306 (15)	141 (17)	129 (15)	36 (12)
Missing	753 (38)	324 (39)	328 (37)	101 (34)

eGFR, estimated glomerular filtration rate.
*Columns my not equal 100% due to rounding. Estimated GFR for E1, E2, and E3 were ≥ 90, 60–89, and 30–59 ml/min/1.73 m^2, respectively.

eGFR categories overlap, so there is no significant difference between groups.

DISCUSSION

This retrospective analysis used data extracted from the EHR to model the changes in eGFR for patients who visited a clinic that prescribed an LCD. Based on eGFR as calculated by the CKD-EPI equation, patients were categorized as E1, E2, and E3. Over one year, regardless of the weight change, for patients with mildly reduced and moderately to severely reduced kidney function (E2 and E3, respectively), eGFR was either unchanged or improved; whereas the eGFR for patients with normal or elevated kidney function (E1), eGFR was decreased by 4–6 ml/min/1.73 m^2. However, for those with moderately to severely reduced kidney function (E3) without diabetes, greater weight loss (i.e., greater LCD adherence) was associated with improvement in eGFR.

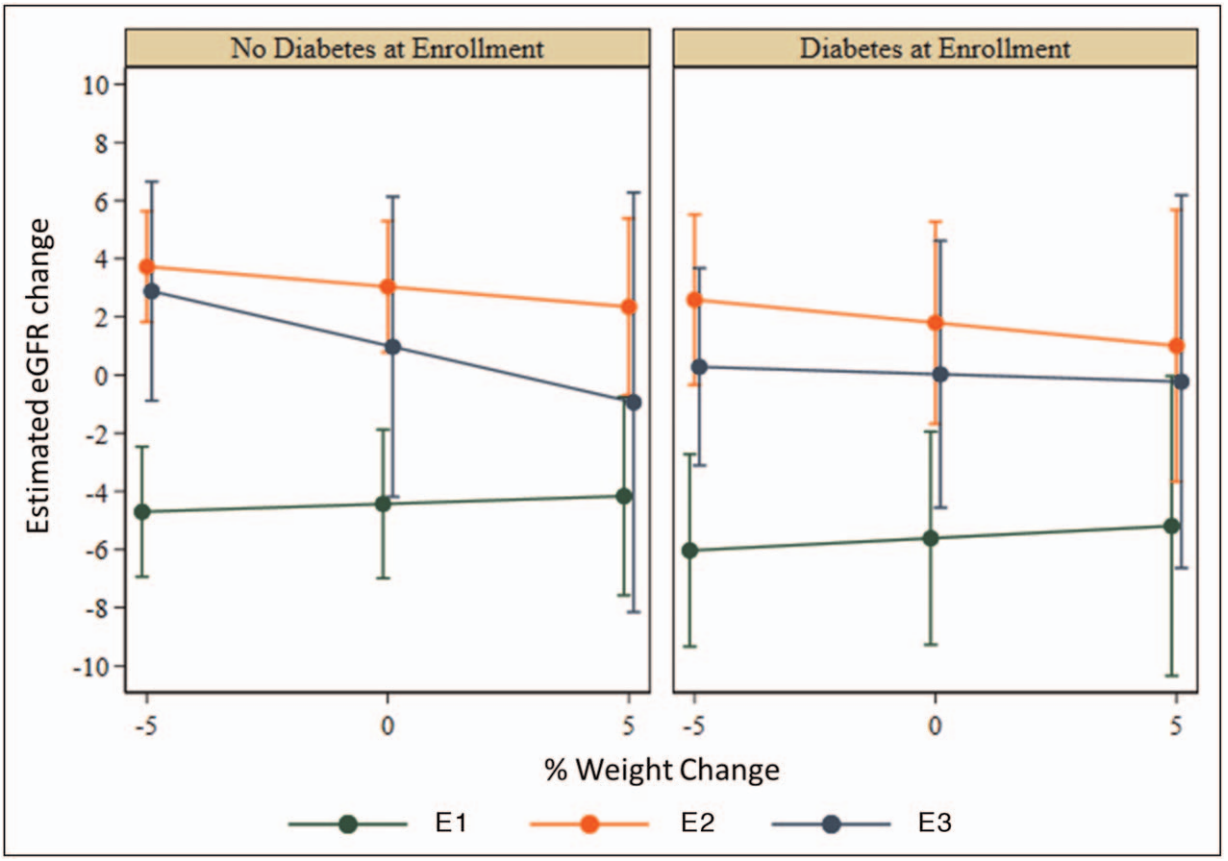

FIGURE 2. Estimated change in eGFR by weight change, eGFR category, and diabetes status for model 2.
Note: Estimated eGFR change from model including main effects and interaction terms for CKD stage, initial diabetes status, and % weight change, with adjustment terms for continuous initial age and BMI and binary sex (M/F). Model evaluated at the estimation sample group means for age, sex, and BMI; remaining model terms as shown. Model $N = 606$.

After age 35, the normal annual eGFR decline associated with aging is about 1 mL/min/1.73 m^2 [19,20]. Although the eGFR decrease predicted for those in category E1 could be considered excessive, it was predicted whether they lost weight or not, and therefore does not appear to be related to LCD adherence. It is unclear why the model predicted a decline for those in category E1 and not the other categories. For example, since we do not know who had albuminuria, these results may be driven by patients with albuminuria. In a prospective non-interventional cohort study, high protein intake was not associated with a decline in eGFR for women with eGFR $\geq$ 80 mL/min/1.73 m^2 (eGFR category E1 and E2); on the other hand, for those with eGFR 55 and <80 mL/min/1.73 m^2 (eGFR categories E2 and E3), higher protein intake was associated with eGFR decline. However, the study did not report corresponding weight change, which can affect eGFR for reasons noted below [21]. In our study, the predicted decline for those in category E1 may be a result of the resolution of hyperfiltration, either through weight loss or improved diabetes control, or loss of glomerular function.

Although GFR decline is associated with natural aging, it is also exacerbated by elevated blood pressure [22], insulin [15], and blood glucose [23]. Clinically significant weight loss, 5% or more, can improve blood pressure, insulin, and blood glucose. In the short term, LCDs are associated with lower blood glucose, which leads to decreased insulin levels, which leads to increased diuresis and natriuresis, which can reduce blood pressure [24,25], and similar effects may be seen in sodium glucose cotransporter-2 (SGLT2) inhibitors [26]. Therefore, LCDs may not impair eGFR for those whose age-related decline is worsened by hypertension and diabetes. One meta-analysis found that compared to individuals on control diets without CKD, those on LCDs experienced a small increase in eGFR [27]. Another meta-analysis of individuals with type II diabetes mellitus found that a low carbohydrate diet did not adversely affect the kidney function [28].

Because there are relatively few pharmacological options to treat patients who are affected by the renal consequences of obesity and diabetes, this study is important. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are commonly used in patients with diabetes, CKD, and hypertension because they have been shown to reduce albuminuria and decrease progression of CKD [29–31]. SGLT2 inhibitors show promising results for patients with diabetes and CKD [32–36,37▪]. However, use of these medications can be limited because of allergic reactions, such as angioedema; other side effects, like chronic urinary tract infections; or high costs. Therefore, it is important to understand if the LCD either worsens or improves GFR in patients with CKD, and we need evidence about the kidney-related risks or benefits of LCDs.

This study has several limitations. First, it is a retrospective analysis of EHR data, and does not include specific outcome measures at designated time points. Second, there are missing data for those who did not return to the clinic and those patients without outcome values. Since analyses cannot account for these types of missing data, results may not generalize to patients without a return visit or serum creatinine data. Additionally, more complete data would be a goal of future prospective studies to validate these exploratory results. Third, kidney function is only assessed by eGFR as calculated with the CKD-EPI equation and does not include quantification of urine protein; hence, we could not identify all patients with CKD in our cohort. Fourth, there is also a recent call for race to be removed from the calculation for eGFR, as in the CKD-EPI equation [38]. Even though race was used to determine eGFR, the variable does not change and should not have caused a difference in the eGFR calculation in the baseline and Q4 periods. Fifth, we did not have direct measures of dietary adherence, so we used weight loss as a proxy measure for dietary change. However, since eGFR did not differ across weight change category, an LCD did not seem to adversely affect the eGFR. Finally, weight loss may also have been due to some other reason, including other dietary changes, increased physical activity, or unintentional weight loss due to illness.

This study has several strengths. First, it includes outcomes on over 2000 individuals. Second, the analysis was a low-risk way to examine the association between an LCD and eGFR. Third, the data were collected in a real-world setting and begins to establish the real-world safety of the LCD in patients with CKD.

CONCLUSION

Obesity and weight-related comorbidities such as diabetes and CKD continue to adversely affect health. We need to understand if LCDs can be used to treat obesity in patients with reduced kidney function. Our results indicate that an LCD does not seem to be associated with adverse effects on eGFR in patients with normal to moderately-to-severely reduced kidney function. To better understand how kidney function is affected by an LCD, future studies should prospectively measure dietary

adherence and physical activity and directly measure changes in GFR and albuminuria for participants with CKD before and during that diet.

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None.

Conflicts of interest

There are no conflicts of interest.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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