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Long-Term Effects of a Very Low Carbohydrate Compared With a High Carbohydrate Diet on Renal Function in Individuals With Type 2 Diabetes

A Randomized Trial

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Abstract: To compare the long-term effects of a very low carbohydrate, high-protein, low saturated fat (LC) diet with a traditional high unrefined carbohydrate, low-fat (HC) diet on markers of renal function in obese adults with type 2 diabetes (T2DM), but without overt kidney disease.

One hundred fifteen adults (BMI 34.6 ± 4.3 kg/m^2, age 58 ± 7 years, HbA1c $7.3 \pm 1.1\%$, 56 ± 12 mmol/mol, serum creatinine (SCr) 69 ± 15 µmol/L, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration formula (eGFR 94 ± 12 mL/min/1.73 m^2)) were randomized to consume either an LC (14% energy as carbohydrate [CHO < 50 g/day], 28% protein [PRO], 58% fat [<10% saturated fat]) or an HC (53% CHO, 17% PRO, 30% fat [<10% saturated fat]) energy-matched, weight-loss diet combined with supervised exercise training (60 min, 3 day/wk) for 12 months. Body weight, blood pressure, and renal function assessed by eGFR, estimated creatinine clearance (Cockcroft–Gault, Salazar–Corcoran) and albumin excretion rate (AER), were measured pre- and post-intervention.

Both groups achieved similar completion rates (LC 71%, HC 65%) and reductions in weight (mean [95% CI]; -9.3 [-10.6, -8.0] kg) and blood pressure (-6 [-9, -4]/-6[-8, -5] mmHg), $P \geq 0.18$. Protein intake calculated from 24 hours urinary urea was higher in the LC than HC group (LC 120.1 ± 38.2 g/day, 1.3 g/kg/day; HC 95.8 ± 27.8 g/day, 1 g/kg/day), $P < 0.001$ diet effect. Changes in SCr (LC 3 [1, 5], HC 1 [-1, 3] µmol/L) and eGFR (LC -4 [-6, -2], HC -2 [-3, 0] mL/min/1.73 m^2) did not differ between diets ($P = 0.25$). AER decreased independent of diet composition (LC $--2.4$ [-6, 1.2], HC -1.8 [-5.4, 1.8] mg/24 h, $P = 0.24$); 6 participants (LC 3, HC 3) had moderately elevated AER at baseline (30–300 mg/24 h), which normalized in 4 participants (LC 2, HC 2) after 52 weeks.

Compared with a traditional HC weight loss diet, consumption of an LC high protein diet does not adversely affect clinical markers of renal function in obese adults with T2DM and no preexisting kidney disease.

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Abbreviations: AER = albumin excretion rate, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration, CrC = creatinine clearance, CVD = cardiovascular disease, DKD = diabetic kidney disease, eGFR = estimated glomerular filtration rate, FFM = fat free mass, HC diet = high carbohydrate, low-fat diet, LC diet = very low carbohydrate, high protein, low saturated fat diet, SCr = serum creatinine, T2DM = type 2 diabetes mellitus.

INTRODUCTION

Concerns exist about the safety of protein-rich diets for renal function, particularly in populations with type 2 diabetes mellitus (T2DM) who are at risk of nephropathy.[1] Despite this, very low carbohydrate, high protein, high fat (LC) diets are rising in popularity amongst individuals with T2DM based on growing evidence of their efficacy as a weight management strategy to improve glycemic control and reduce cardiovascular disease (CVD) risk.[2] Few well-controlled, long-term studies have systematically examined the effects of LC diets as part of a comprehensive lifestyle modification program on renal function in T2DM, limiting the applicability of LC diets as a diabetes management strategy. This study compares the effects, after 1 year of consumption of a novel energy-restricted LC diet that limits saturated fat, with an energy-matched traditional high unrefined carbohydrate, low-fat (HC) diet whilst undertaking a supervised exercise program, on renal function in obese adults with T2DM and without diabetic kidney disease (DKD).

MATERIALS AND METHODS

Participants and Study Design

Enrollment criteria, study design, and the primary study outcomes have been previously described.[2] Briefly, 115 adults with T2DM and without overt kidney disease (57% male (mean ± SD) BMI 34.6 ± 4.3 kg/m^2, age 58 ± 7 years, HbA1c 7.3 ± 1.1%, 56 ± 12 mmol/mol, serum creatinine (SCr) 69 ± 15 μmol/L, glomerular filtration rate estimated by the Chronic Kidney Disease Epidemiology Collaboration formula (eGFR-CKD-EPI) 94 ± 12 mL/min/1.73 m^2) were recruited by public advertisement. Exclusion criteria were type-1 diabetes; preexisting renal disease (eGFR < 60 mL/min/1.73 m^2, elevated SCr > 120 μmol/l, and/or albumin excretion rate (AER) > 300 mg/24 h); abnormal liver function; any significant endocrinopathy (other than stable treated thyroid disease); history of malignancy, respiratory, gastrointestinal, or CVD; pregnancy/lactation; history of/or current eating disorder or smoking. The study was approved by the Human Research Ethics Committees of the Commonwealth Scientific and Industrial Research Organisation and the Universities of Adelaide and South Australia. All participants gave written informed consent.

In a parallel design, participants were randomized to consume either a hypocaloric (500–1000 kcal/day deficit) LC diet (14% energy as carbohydrate [CHO < 50 g/day], 28% protein [PRO], 58% fat [<10% saturated fat]) or an energy-matched HC diet (53% CHO, 17% PRO, 30% fat [<10% saturated fat]); combined with supervised aerobic/resistance exercise (60 minutes, 3 day/wk) for 12 months. Detailed description of the diets, exercise program and the effects of the dietary interventions on body weight, glycemic control, and CVD risk factors have been reported elsewhere.[2]

Body Weight, Blood Pressure, HbA1c, Renal Function Measures, and Protein Intake

Body weight was measured using calibrated electronic scales (Mercury AMZ1, Tokyo, Japan) at baseline and monthly intervals. Other outcomes were assessed at weeks 0, 24, and 52. Seated blood pressure was measured by automated sphygmomanometry (SureSigns VS3; Phillips, Andover, MA). HbA1c was measured at a certified pathology laboratory (Institute of Medical and Veterinary Science Pathology, Adelaide, Australia). Outcomes were assessed in the clinic after an overnight fast, with water consumed as required to avoid dehydration.

SCr was measured on a clinical analyzer (Beckman AU480; Beckman Coulter, Inc., Brea, CA) using a standardized assay (Beckman kit #OSR6178). eGFR (mL/min/1.73 m^2) was calculated according to CKD-EPI Eq.[3] which has greater accuracy compared to the Modification of Diet in Renal Disease (MDRD) equation at higher GFR (>60 mL/min/1.73 m^2).[4] Creatinine clearance (CrCl, mL/min) was estimated using the Cockcroft–Gault equation[5] with fat free mass (FFM—whole-body dual-energy X-ray absorptiometry, Lunar Prodigy; General Electric Corporation, Madison, WI) adjustment to improve estimation in obesity,[6] and the Salazar–Corcoran Eq.[7] developed for use in obese individuals based on estimated FFM. AER, urinary albumin, and urea obtained from 24 hours urine samples were measured at a certified commercial laboratory (Institute of Medical and Veterinary Science Pathology, Adelaide, Australia).

Protein intake (g/day) was estimated from 24 hours urinary urea excretion at weeks 0, 24, and 52.[8,9] Dietary compliance was assessed randomly from 7 consecutive days of daily weighed food records for every 14-day period, analyzed using Foodworks Professional Edition Version 7 (Xyris Software 2012, Highgate Hill, Australia). Both dietary patterns achieved a high level of compliance as reported.[2]

Statistical Analyses

Baseline group differences were compared by independent t tests and χ^2 tests for continuous and categorical variables, respectively. AER and urinary albumin were reciprocally transformed to improve normality before analysis. Comparisons of changes over time between diets were analyzed by random-coefficient analysis, restricted maximum likelihood, mixed effects model using an unstructured covariance with data assumed to be missing at random. The model included all available data from participants who commenced the study and contained the following fixed effects: main effect for each time-point, diet group assignment, and diet group by time-point interaction. The effect of the use of renin-angiotensin system blocking agents including angiotensin-converting-enzyme inhibitors and angiotensin receptor antagonists on the renal outcomes investigated was examined in sensitivity analyses that included this as a covariate. Estimated marginal means (95% confidence intervals, CI) and change from weeks 0 to 52 are reported. Repeated measures ANOVA with diet as between-subjects factor and time as within-subject factor was used to assess changes in dietary protein intake. All analyses were performed using SPSS 20.0 for Windows (SPSS, Inc., Chicago, IL); statistical tests were 2-tailed with statistical significance at $P < 0.05$.

RESULTS

At baseline, there were no significant clinical or biochemical differences between groups (Table 1). SCr and eGFR were within the normal range (Table 2); 7 participants (LC:4, HC:3) had moderately increased AER (30–300 mg/24 h).[10] Antihypertensive therapy use was similar in both groups (LC:41, HC:35, $P = 0.29$) with 56% of participants using renin-angiotensin system blocking agents (LC:32, HC:32). Sixty-eight percent of participants completed the study with no difference between groups (LC:41/58, HC:37/57; $P = 0.51$).

Over the 52 weeks, reductions in weight and blood pressure were comparable between groups ($P \geq 0.18$; Table 2). Nine participants reduced (LC:4, HC:5) and 3 increased (LC:2, HC:1) use of renin-angiotensin system blocking agents.

Self-reported protein intake was higher in LC compared to HC (LC:106.1 ± 18.9 g/d (26% energy), 1.2 g/kg/d; HC:78.5 ± 14.8 g/d (18% energy), 0.9 g/kg/d), $P < 0.001$. Protein intakes estimated from 24 hours urinary urea reflected similar differences (weeks 0, 24, and 52; LC: 112.1 ± 34.3, 118.4 ± 33.8, 120.1 ± 38.2 g/d; 1.1 ± 0.3, 1.4 ± 0.4, 1.3 ± 0.4 kg/d; HC: 107.7 ± 28.4, 89.8 ± 18.4, 95.8 ± 27.8 g/d; 1.0 ± 0.3, 1.0 ± 0.2, 1.1 ± 0.3 g/kg/d; $P < 0.001$).

Over time, SCr increased, while eGFR, CrCl, and AER decreased, with no difference in the responses between groups (Table 2). Sensitivity analyses that adjusted for the use of renin-angiotensin system blocking agents did not alter the results of the primary model. At baseline, 7 participants (LC:4, HC:3) had pathological albuminuria (range 41–101 mg/24 h). After 52 weeks, 4 of these participants (LC:2, HC:2) became normoalbuminuric, 2 (LC:1, HC:1) remained pathologically albuminuric, and 1 LC participant withdrew before week 52. All participants who were normoalbuminuric at baseline remained so after 52 weeks.

TABLE 1. Baseline Participant Characteristics[*]

	LC Diet (n = 58)	HC Diet (n = 57)
Demographics		
Age	58 (7)	58 (7)
Sex [n (%)]		
Females	21 (36)	28 (49)
Males	37 (64)	29 (51)
Duration of diabetes (years)	7 (5)	9 (7)
Body weight and BMI		
Body weight (kg)	101.7 (14.4)	101.6 (15.8)
BMI (kg/m^2)	34.2 (4.5)	35.1 (4.1)
Glycemic control		
HbA1c (%)	7.3 (1.1)	7.4 (1.1)
CVD risk markers		
SBP (mm Hg)	130.4 (13.1)	132.6 (13.2)
DBP (mm Hg)	80.0 (8.9)	80.8 (10.1)
Fasting insulin (mU/L)[†]	16.3 (8.3)	15.9 (7.6)
HOMA2-IR[†]	2.3 (1.1)	2.2 (1.0)
HOMA2-%B[†]	75.5 (38.7)	67.7 (33.4)
Total Cholesterol (mmol/L)	4.5 (1.0)	4.3 (1.0)
LDL-C (mmol/L)	2.5 (0.9)	2.4 (0.9)
HDL-C (mmol/L)	1.2 (0.2)	1.3 (0.3)
TG (mmol/L)	1.6 (0.7)	1.4 (0.6)
Medications		
[0,1-3] Diabetes medications		
Insulin [n (%)]	6 (10)	6 (11)
Metformin [n (%)]	46 (79)	41 (72)
Sulfonylureas [n (%)]	20 (34)	16 (28)
Thiazolidinediones [n (%)]	3 (5)	3 (5)
GLP-1 agonists [n (%)]	1 (2)	1 (2)
DPP-4 inhibitors [n (%)]	1 (2)	2 (4)
Antihypertensive medications [n (%)]	41 (71)	35 (61)
ACE-inhibitors [n (%)]	20 (34)	19 (33)
Angiotensin-II receptor antagonists [n (%)]	14 (24)	13 (23)
Calcium channel blockers [n (%)]	18 (31)	12 (21)
Beta blockers [n (%)]	6 (10)	3 (5)
Lipid lowering medications [n (%)]	35 (60)	36 (63)

Data are means (SD), unless otherwise stated.

To convert mmol/L to mg/dL, multiply by 38.7 (for cholesterol) and 88.6 (for triglycerides).

ACE-inhibitors = angiotensin-converting-enzyme inhibitors; BMI = body mass index; DBP = diastolic blood pressure; DPP-4 inhibitors = dipeptidyl-peptidase-4 inhibitors; GLP-1 agonists = glucagon-like peptide-1 agonists; HC diet = high carbohydrate, low-fat diet; HDL-C = high density lipoprotein cholesterol; HOMA2-%B = homeostasis model of assessment index 2-β cell function; HOMA2-IR = homeostasis model of assessment index 2-insulin resistance; LC diet = very low carbohydrate, high protein/low saturated fat diet; LDL-C = low density lipoprotein cholesterol; SBP = systolic blood pressure; TG = triglycerides.

[*] Total analyzed n = 115 (LC:58, HC:57) for all data unless otherwise stated. All baseline characteristics were not significantly different between diet groups ($P > 0.05$) by independent samples *t* test (continuous variables) or χ^2 test (categorical variables).

[†] Total analyzed n = 103 (LC:52, HC:51) for insulin and HOMA2 data; 12 participants on insulin medication at baseline were excluded from analyses.

DISCUSSION

GFR and albuminuria are established indicators of the presence and progression of DKD.[10] This study showed these markers responded similarly following consumption of either energy-matched LC or HC weight-loss diets administered as part of a holistic lifestyle modification program incorporating regular exercise. The overall conclusion was not altered after controlling for antihypertensive treatment. Within the limits of a modest sample size, our results in obese adults with T2DM, but without overt DKD, confirm and extend the findings of previous investigations conducted in people without diabetes and

individuals with preexisting DKD.[11–14] The literature supporting the utility of protein restriction in slowing GFR decline or delaying DKD progression is controversial. Acknowledging the limitations of observational studies (such as the possibility of unaccounted residual confounding), prospective cohort studies of people with T2DM and without DKD at baseline have found no association between protein intake and eGFR decline,[15] or a negative association between protein intake and risk of DKD.[16] Although earlier meta-analyses have reported a small but statistically significant reduction in GFR decline and incidence of renal failure or death from dietary protein restriction, only a

TABLE 2. Estimated Marginal Means and Changes (95% CI) in Weight, Blood Pressure, Albuminuria, Serum Creatinine, Estimated Glomerular Filtration Rate, and Creatinine Clearance at Baseline and After 52 weeks on a Very Low Carbohydrate, High Protein, Low Saturated Fat (LC) Diet or an Isocaloric High Carbohydrate, Low-Fat (HC) Diet*

	LC Diet			HC Diet			P-Value†
	Week 0	Week 52	Change‡	Week 0	Week 52	Change‡	
Body weight and blood pressure							
Body weight (kg)‡	101.7 (97.8 to 105.7)	92.0 (87.9 to 96.1)	−9.8 (−11.7 to −7.9)	101.6 (97.6 to 105.6)	91.5 (87.3 to 95.6)	−10.1 (−12.0 to −8.2)	0.18
SBP (mm Hg)‡	130.4 (126.9 to 133.8)	123.2 (119.5 to 127.0)	−7.1 (−10.6 to −3.7)	132.6 (129.1 to 136.0)	126.8 (122.9 to 130.6)	−5.8 (−9.4 to −2.2)	0.81
DBP (mm Hg)‡	80.0 (77.5 to 82.4)	73.8 (71.4 to 76.1)	−6.2 (−8.2 to −4.1)	80.8 (78.2 to 83.3)	74.4 (72.0 to 76.8)	−6.4 (−8.4 to −4.3)	0.38
Renal markers							
Serum creatinine (μmol/L)‡	69 (65 to 72)	72 (68 to 76)	3 (1 to 5)	71 (67 to 75)	72 (68 to 76)	1 (−1 to 3)	0.25
Urinary albumin (mg/L)‡,§	3.3 (1.1 to 5.4)	1.8 (0.7 to 2.9)	−1.4 (−3.1 to 0.2)	2.4 (0.3 to 4.5)	1.6 (0.5 to 2.7)	−0.8 (−2.4 to 0.9)	0.21
AER (mg/24 h)‡,§	6 (2 to 11)	4 (2 to 6)	−2 (−6 to 1)	5 (1 to 9)	3 (1 to 6)	−1.8 (−5 to 2)	0.24
eGFR-CKD-EPI‡,|| (mL/min/1.73 m²)	96 (93 to 99)	92 (89 to 95)	−4 (−6 to −2)	92 (88 to 94)	90 (87 to 93)	−2 (−3 to 0)	0.25
CrCl-Cockcroft–Gault‡,¶ (mL/min)	88 (83 to 93)	80 (76 to 85)	−8 (−10 to −5)	82 (77 to 87)	77 (72 to 81)	−5 (−8 to −3)	0.32
CrCl-Salazar–Corcoran‡,# (mL/min)	127 (119 to 134)	113 (107 to 120)	−13 (−17 to −10)	120 (112 to 127)	109 (103 to 115)	−11 (−14 to −7)	0.50

Data are estimated marginal means (95% confidence intervals) by linear mixed-effects model analysis.

AER = albumin excretion rate; CKD-EPI = chronic kidney disease epidemiology collaboration; CrCl = creatinine clearance; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; HC diet = high carbohydrate, low-fat diet; LC diet = very low carbohydrate, high protein, low saturated fat diet; SBP = systolic blood pressure.

To convert μmol/L to mg/dL, multiply by 0.0113 (for serum creatinine).

* Total analyzed n = 115 (LC:58, HC:57) for all data unless otherwise stated.

† P-value refers to between group differences over time (diet × time interaction) by linear mixed-effects model analysis.

‡ P < 0.05 significant change from baseline to 52 weeks (time effect).

§ Total analyzed n = 113 (LC:56, HC:57) for urinary albumin and AER data; no urine analyses were available at baseline for 2 participants in the LC diet group.

|| eGFR-CKD-EPI (mL/min/1.73 m²)³ = 141 × min (SCr(mg/dL)/κ, 1)$^{\alpha}$ × max(SCr(mg/dL)/κ, 1)$^{-1.209}$ × 0.993$^{\text{Age}}$[x1.018 if female][x1.159 if black]. where κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of SCr/κ or 1 and max indicates the maximum of SCr/κ or 1.

¶ CrCl-Cockcroft–Gault (mL/min)⁵ = [140−age(years)] × FFM(kg)/(SCr (mg/dL) × 72) [x0.85 if female], where FFM is fat free mass.

CrCl-Salazar–Corcoran (mL/min)⁷ = [137−age(years)] × {[0.285 × weight(kg)] + [12.1 × height(m)²]}÷A/[51 × SCr(mg/dL)] for males; [147−age(years)] × {[0.287 × weight(kg)] + [9.74 × height(m)²]}÷[60 × SCr(mg/dL)] for females

small number of people with diabetes (predominantly T1DM) were studied and nonrandomized trials were included.[17–19] Moreover a reduced risk of renal failure attributed to low protein diets might reflect a delayed initiation of dialysis due to amelioration of uremic symptoms rather than an actual retardation of renal function decline. A recent meta-analysis of randomized controlled trials showed that a low protein diet was not associated with a significant improvement in renal function in people with DKD when compared with a normal protein diet (0.9 g/kg/day cf. 1.3 g/kg/day).[20] The present study did not specifically examine a low protein diet (0.8 g/kg/day, 16–18% total energy) recommended by current clinical guidelines for individuals with DKD.[21] However, actual protein intakes reported in low protein intervention groups have typically ranged from 0.7 to 1.1 g/kg/d[19,20] which includes the mean protein intake range of the comparison HC diet group in this study (1–1.1 g/kg/d) that more likely reflects a typical protein intake. Collectively, these data suggest that compared to a traditional HC diet, consumption of an LC, high protein diet (1.1–1.4 g/kg/d) derived from both plant and animal protein sources, does not adversely affect renal function in individuals with T2DM. This raises the clinical relevance of LC diets as a tenable weight management strategy for individuals with T2DM and comorbidities like hypertension and dyslipidemia, to improve glycemic control and reduce CVD and diabetes complications risk.[2]

Irrespective of any differences between the diets, both groups experienced an overall reduction in eGFR and CrCl despite substantial weight loss (9.1%), improvement in glycemic control (HbA1c −1%, −10.9 mmol/mol), reductions in blood pressure (−6/−6 mm Hg) and albuminuria.[2] The 2% to 4% decrease in eGFR observed in the present study is compatible with the expected age-related change in eGFR in T2DM[22,23] and is unlikely to be clinically significant. Previous studies that reported declines in eGFR following weight loss have examined individuals without renal impairment,[11,14] compared to those that reported increases in eGFR that examined individuals with preexisting renal dysfunction.[13,14] This suggests that weight loss-induced increases in eGFR may more likely occur in populations with preexisting renal dysfunction, a phenomenon that has also been observed postbariatric surgery.[24] Moreover, the overall reduction in albuminuria over time and the normalization of levels in patients with albuminuria at baseline support the benefits of weight loss.[25]

A limitation of this study was that GFR was estimated rather than directly measured. Clearance of inulin and radio-isotope-labeled filtration markers (iGFR) are considered ''gold standards'' for measuring GFR. Nevertheless, equations for eGFR and CrCl are used widely in clinical practice for drug dosing, screening, risk stratification and for monitoring DKD progression. The equations used in this study have been validated in obese populations, including individuals with diabetes and conferred greater accuracy compared with other equations against iGFR.[6] Hence, this methodological approach is considered appropriate for the purpose of comparing the long-term renal effects of differing diet regimens.

Variations in determinants of creatinine generation (eg, FFM, exercise, and diet) can also influence eGFR calculations. The combined effect of a similar FFM loss (−1.7 kg) and increase in moderate to vigorous exercise[2] could explain the increase in SCr[26] and consequent reductions in creatinine-based eGFR calculations observed in both groups, potentially masking any diet-induced differences in renal function. Changes in body composition and the nonsteady-state clearance of endogenous filtration markers expose the limitations of existing methods and the complexity of assessing renal function after weight loss. The use of combined creatinine-cystatin C equations may improve precision by minimizing the influence of any particular non-GFR determinant.[27,28]

In conclusion, a hypocaloric LC diet and an energy-matched traditional HC diet had similar effects on markers of renal function in people with T2DM without DKD over a 12-month period. These results corroborate evidence that consumption of an LC weight loss diet does not adversely affect renal function in such populations. Longer-term follow-up studies are required to determine whether these renal effects are sustained during long-term weight loss maintenance and to establish if long-term adherence to the diets results in differences in the development and progression of DKD. Examining the effects of LC diets in populations with preexisting vascular complications besides nephropathy would further advance our understanding of the utility of LC diets.

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