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Renal Function Following Long-Term Weight Loss in Individuals with Abdominal Obesity on a Very-Low-Carbohydrate Diet vs High-Carbohydrate Diet

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ABSTRACT

A frequently cited concern of very-low-carbohydrate diets is the potential for increased risk of renal disease associated with a higher protein intake. However, to date, no well-controlled randomized studies have evaluated the long-term effects of very-low-carbohydrate diets on renal function. To study this issue, renal function was assessed in 68 men and women with abdominal obesity (age 51.5±7.7 years, body mass index [calculated as kg/m^2] 33.6±4.0) without preexisting renal dysfunction who were randomized to consume either an energy-restricted (~1,433 to 1,672 kcal/day), planned isocaloric very-low-carbohydrate (4% total energy as carbohydrate [14 g], 35% protein [124 g], 61% fat [99 g]), or high-carbohydrate diet (46% total energy as carbohydrate [162 g], 24% protein [85 g], 30% fat [49 g]) for 1 year. Body weight, serum creatinine, estimated glomerular filtration rate and urinary albumin excretion were assessed before and after 1 year (April 2006-July 2007). Repeated measures analysis of variance was conducted. Weight loss was similar in both groups (very-low-carbohydrate: −14.5±9.7 kg, high-carbohydrate: −11.6±7.3 kg; P=0.16). By 1 year, there were no changes in either group in serum creatinine levels (very-low-carbohydrate: 72.4±15.1 to 71.3±13.8 μmol/L, high-carbohydrate: 78.0±16.0 to 77.2±13.2 μmol/L; P=0.93 time × diet effect) or estimated glomerular filtration rate (very-low-carbohydrate: 90.0±17.0 to 91.2±17.8 mL/min/1.73 m^2, high-carbohydrate: 83.8±13.8 to 83.6±11.8 mL/min/1.73 m^2; P=0.53 time×diet effect). All but one participant was classified as having normoalbuminuria at baseline, and for these participants, urinary albumin excretion values remained in the normoalbuminuria range at 1 year. One participant in high-carbohydrate had microalbuminuria (41.8 μg/min) at baseline, which decreased to a value of 3.1 μg/min (classified as normoalbuminuria) at 1 year. This study provides preliminary evidence that long-term weight loss with a very-low-carbohydrate diet does not adversely affect renal function compared with a high-carbohydrate diet in obese individuals with normal renal function.

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In response to the obesity epidemic, there has been increased public interest and use of alternative weight-loss diets that contravene conventional dietary guidelines. Popular alternatives include very-low-carbohydrate diets, which have a common theme of restricting carbohydrate intake (<20 to 50 g/day) while increasing fat and protein (1,2).

Previous studies have shown that, compared to conventional high-carbohydrate, low-fat diets that have >45% of total calories from carbohydrates, a very-low-carbohydrate diet produced greater weight loss over 6 months and at least comparable weight loss over 12 months (3-5). An often cited concern of very-low-carbohydrate diets is the potential for increased risk of renal disease associated with higher protein intake (6-8). However, to date, there have been no well-controlled randomized studies evaluating the long-term effects of very-low-carbohydrate diets on renal function. In an uncontrolled, single-arm, 6-month intervention, no changes in urinary creatinine clearance or protein excretion were observed following a very-low-carbohydrate diet (9). Similarly, other studies have also reported no differences in renal function between a very-low-carbohydrate or high-carbohydrate diet after periods up to 24 weeks in overweight and obese patients who were either generally healthy or who had type 2 diabetes (10-12). However, inferences that can be drawn from these studies about the long-term effects are limited by

Very low-carbohydrate, high-fat diet (1,433 kcal)	High-carbohydrate, low-fat diet (1,433 kcal)
125 mL full-fat milk	300 mL nonfat milk
70 g full-fat cheddar cheese	2 slices whole-grain bread (40 g/slice)
1 medium (50-55 g) egg	40 g high-fiber cereal (eg, All Bran, Sultana Bran [Kellogg's, Pagewood, NSW, Australia])
300 g (raw weight) beef, chicken, fish	20 g reduced-fat cheese (2 times/week)
100 g (cooked weight) ham, tuna, beef, chicken, turkey	150 g (raw weight) beef, chicken, pork, lamb (5 times/week)
At least 2.5 cups (green) vegetables	300 g fruit
25 g (5 tsp) oil/butter	150 g fish (once/week)
40 g raw, unsalted mixed nuts	At least 2.5 cups vegetables
2 standard alcoholic drinks/week (optional)	1 medium potato (3 times/week)
	100 g (dry weight) pasta/rice (4 times/week)
	100 g bean/lentils (2 times/week)
	200 g nonfat yogurt (3 times/week)
	20 g raw unsalted nuts
	50 g tinned fish (3 times/week)
	2 tsp polyunsaturated margarine
	3 tsp vegetable oil, eg, olive or canola oil
	2 standard alcoholic drinks/week (optional)

Figure. Food profile of very-low-carbohydrate, high-fat diet and the high-carbohydrate, low-fat diet.

their relatively short duration (9-12), or the lack of an appropriate control group (9). The purpose of the present study was to assess the long-term effects of an energy-restricted very-low-carbohydrate diet and a conventional high-carbohydrate, low-fat diet on renal function. It was hypothesized that relative to the high-carbohydrate diet, a very-low-carbohydrate diet would adversely affect renal function.

METHODS

Participants and Study Design

The enrollment criteria, study design, and primary study outcomes have been described elsewhere (3). Briefly, 118 participants (122 recruited, four withdrew prior to randomization) aged 24 to 64 years with abdominal obesity (waist circumference: ≥94 cm men, ≥80 cm women) and at least one additional metabolic syndrome risk factor (13) were recruited by public advertisement. Exclusion criteria were a history of liver, respiratory, gastrointestinal, cardiovascular, or peripheral vascular disease; diabetes; pregnancy; or cancer. Participants were randomized to consume either an energy-restricted very-low-carbohydrate diet (n=57) or an isocaloric conventional high-carbohydrate diet (n=61) for 52 weeks. The study was approved by the Human Research Ethics Committees of the Commonwealth Scientific and Industrial Research Organisation and the University of South Australia. All participants provided written informed consent prior to participation (trial registration: anzctr.org.au identifier: 12606000203550).

Dietary Intervention and Compliance

Both diets were designed to be isocaloric with moderate energy restriction (~1,433 to 1,672 kcal/day). The planned macronutrient profiles of the dietary patterns were as follows: very-low-carbohydrate diet (4% of total energy as carbohydrate [14 g], 35% protein [124 g], and 61% fat [99 g]) and high-carbohydrate (46% of total energy as carbohydrate [162 g], 24% protein [85 g], and 30% fat [49 g]). To achieve the specified macronutrient profiles and energy levels, the dietary patterns were structured into prescriptive dietary plans of specific food quantities (Figure). These plans were presented to the participants in a quantitative food record that they completed daily. Participants were asked to weigh and measure their food daily using scales that were provided. Participants also met individually with a research dietitian every 2 weeks for the first 8 weeks and monthly thereafter for detailed dietary advice, meal plans, and recipe information pertaining to each diet. Dietary compliance was assessed on the basis of 3 days from the food records (2 weekday and 1 weekend day) within each consecutive 2-week period for the duration of the study using computerized dietary software (Foodworks Professional Edition, version 4, 1998, Xyris Software, Highgate Hill, Queensland, Australia). Throughout the intervention, urinary urea excretion was also measured to assess protein intake and plasma ketone concentrations to monitor compliance to carbohydrate restriction in the very-low-carbohydrate diet group. A high level of dietary compliance was achieved with both dietary patterns, as reported previously (3).

Body Weight and Renal Function Measures

Assessments and blood sampling were performed by a research nurse blinded to treatment assignment. Body weight was measured using calibrated electronic digital scales (AMZ14, Mercury, Tokyo, Japan) at baseline and at each diet counseling visit. At weeks 0 and 52, fasting blood samples were also collected into tubes containing no additives for the measurement of serum creatinine. On the day before the scheduled clinic visits at weeks 0 and 52, 24-hour urine samples were collected for the measurement of urinary albumin excretion. All the participants were provided with urine-collection bottles and were pro-

Table. Body weight, serum creatinine, and estimated glomerular filtration rate before and after 52 weeks of energy restriction with either a very-low-carbohydrate, high-fat diet or high-carbohydrate, low-fat diet

	Very-Low-Carbohydrate, High-Fat Diet (n=33)		High-Carbohydrate, Low-Fat Diet (n=35)	
	Week 0	Week 52	Week 0	Week 52
	← mean±standard deviation →			
Weight (kg)	93.9±15.5	79.4±13.6[a]	95.0±12.3	83.5±12.5[a]
Body mass index[b]	33.6±4.0	28.4±3.5[a]	33.5±3.8	29.4±3.9[a]
Serum creatinine (μmol/L)	72.4±15.1	71.3±13.8	78.0±16.0	77.2±13.2
eGFR[c] (MDRD) (mL/min/1.73 m^2)	90.0±17.0	91.2±17.8	83.8±13.8	83.6±11.8
eGFR[d] (Salazar-Corcoran) (mL/min)	113.6±23.4	105.8±23.7[a]	108.7±21.2	101.4±17.7[a]
eGFR[d] (Salazar-Corcoran) (mL/min/1.73 m^2)	97.4±17.0	97.1±17.5	91.8±15.0	90.5±12.3

[a] $P<0.001$ significant change from week 0.
[b] Calculated as kg/m^2.
[c] eGFR (MDRD)=estimated glomerular filtration rate calculated using the Modification in Renal Disease Study formula (15).
[d] eGFR (Salazar-Corcoran)=estimated glomerular filtration rate calculated using the Salazar-Corcoran formula (14).

vided detailed instructions to begin the 24-hour collection immediately after completion of the first void in the morning and to collect all urine for 24 hours, including the final void at the completion of the 24-hour period. Participants were also instructed to record the start and completion times of the sample collection on the specimen bottle and were questioned about the completeness of the sample upon receipt of delivery. Serum creatinine and urinary albumin concentrations were measured on a BM/Hitachi 902 Automatic Analyzer with standard enzymatic kits (Roche Diagnostics Co, Indianapolis, IN). The lower limit of detection for this albumin assay was 3 mg/L.

Two formulas were used to estimate glomerular filtration rate (14,15). One formula was the Modification in Renal Disease Study (MDRD) equation (15): estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2)=186.3×(serum creatinine [mg/dL])$^{-1.154}$×(age)$^{-0.203}$×0.742 (if female). The second equation was a modification of the Cockcroft-Gault formula for estimating creatinine clearance developed by Salazar and Corcoran and validated specifically for use in obese patients (14). The formula for men is: eGFR (mL/min)=(137−age)×[(0.285×weight)+(12.1×height^2)]/(51×creatinine concentration) and for women is: eGFR (mL/min)=(146−age)×[(0.287×weight)+(9.74×height^2)]/(60×creatinine concentration); where age is measured in years, weight in kilograms, height in meters, and creatinine in mg/dL. The Salazar and Corcoran formula provides an estimate of absolute creatinine clearance. Because creatinine clearance is proportional to body surface area, eGFR values were also normalized for body surface area (16), for conventional expression as mL/min/1.73 m^2 to determine relative GFR. This is suitable for assessing and monitoring kidney function in patients with obesity.

Statistical Analysis

Baseline comparisons were made using independent t test for continuous variables and Pearson χ^2 tests for categorical variables. Comparison of changes between diets from baseline to week 52 for weight, serum creatinine, and eGFR were made using repeated measures analysis of variance, with time as the within-participant factor (ie, weeks 0 and 52) and diet (very-low-carbohydrate vs high-carbohydrate) and sex as between-participant factors. Correlational analysis was used to determine relations between variables. Statistical significance was set at an α level of $P<0.05$. All analyses were performed using SPSS for Windows (version 16.0, 2008, SPSS Inc, Chicago, IL). All values cited represent mean±standard deviations, unless otherwise stated.

RESULTS AND DISCUSSION

Of 118 participants randomized to dietary treatment, 49 participants (very-low-carbohydrate, n=24; high-carbohydrate, n=25) dropped out of the study. Of the remaining 69 participants who completed the study, 68 had stored samples for analyses (very-low-carbohydrate, n=33, high-carbohydrate, n=35) and were included in the current investigation. Characteristics were similar between those who completed (completers) and dropped out (dropouts) of the study, including age (completers: 51.4±7.1 years vs dropouts: 48.3±9.0 years), weight (completers: 94.5±13.9 kg vs dropouts: 97.2±16.6 kg), body mass index (calculated as kg/m^2) (completers: 33.5±3.4 vs dropouts: 34.1±4.7), and sex distribution (63% of the completers were women and 64% of the dropouts were women). For those who competed the study, at baseline, both groups were also similarly matched for sex distribution (very-low-carbohydrate [11 men and 22 women], high-carbohydrate [14 men and 21 women]; $P=0.57$), age (very-low-carbohydrate: 51.2±7.7 years, high-carbohydrate: 51.3±6.5 years; $P=0.90$), body weight (very-low-carbohydrate: 93.9±15.5 kg, high-carbohydrate: 95.0±12.3 kg; $P=0.74$), and body mass index (very-low-carbohydrate: 33.6±4.0, high-carbohydrate: 33.5±3.8; $P=0.87$). After 52 weeks, weight loss was, on average, 13.0±8.6 kg (13.5%±8.1%; $P<0.001$ for time), with no significant difference between groups (very-low-carbohydrate: 14.5±9.7 kg, high-carbohydrate: 11.6±7.3 kg; $P=0.16$ time×diet effect) (Table).

On the basis of the results of the food records, total energy intake was similar in both groups (very-low-carbohydrate:

1,613±194 kcal/day, high-carbohydrate: 1,525±184 kcal/day; $P=0.15$), whereas compared to the high-carbohydrate diet group, the very-low-carbohydrate diet group consumed significantly less carbohydrate (very-low-carbohydrate: 31.1±13.1 g/day, high-carbohydrate: 171.7±25.3 g/day; $P<0.001$) and more protein (very-low-carbohydrate: 130.4±11.4 g/day, high-carbohydrate: 84.2±7.7; $P<0.001$) and fat (very-low-carbohydrate: 101.8±14.9 g/day, high-carbohydrate: 45.7±9.4 g/day; $P<0.001$).

Protein intake has long been recognized as a modulator of renal function by which increases in protein intake increase GFR (17-19). Very-low-carbohydrate diets are typically higher in protein than a habitual diet (20), and this has raised concern that chronic consumption of a very-low-carbohydrate diet may affect kidney function by increasing glomerular pressure and hyperfiltration that may lead to progressive loss of renal function (6,7). In the present study, serum creatinine and eGFR calculated using the MDRD equation did not change in either diet group during the intervention ($P\geq0.86$ time×diet interaction, Table). By week 52, using the Salazar-Corcoran formula, absolute eGFR (mL/min) decreased in both groups ($P<0.001$), with no effect of diet ($P=0.86$). The reduction in absolute eGFR (mL/min) correlated with weight loss ($r=0.37$, $P=0.01$) and the reduction in body surface area ($r=0.38$, $P=0.001$) such that relative eGFR expressed conventionally as mL/min/1.73 m^2 did not change in either group during the intervention ($P=0.63$). No significant effect of sex was observed for any of the outcomes. At week 0, urinary albumin excretion values showed all participants (except one participant in the high-carbohydrate diet group) had normoalbuminuria (urinary albumin excretion: ≤19.9 μg/min) (15). For these participants, urinary albumin excretion values remained in the normoalbuminuria range at week 52. For the one participant in the high-carbohydrate group who reported microalbuminuria at week 0 (41.8 μg/min), the urinary albumin excretion decreased to a value of 3.1 μg/min (classified as normoalbuminuria) at week 52. Based on these data, the original hypothesis that a very-low-carbohydrate diet would adversely affect renal function was not supported.

The present results are consistent with the findings of other shorter-term interventional studies, during which participants following a very-low-carbohydrate diet consumed similar protein levels (10,11). These two separate studies (10,11) reported no differences in serum creatinine levels and/or eGFR (calculated using the MDRD equation) in overweight and obese individuals with or without type 2 diabetes following 24 weeks of weight loss with either a very-low-carbohydrate diet (30 to 49 g carbohydrate, 98 to 108 g protein, and 101 to 111 g fat) or a high-carbohydrate diet (149 to 198 g carbohydrate, 67 to 70 g protein, and 49 to 55 g fat). These data are also consistent with a long-term prospective study based on data from the Nurses' Health Study (21), which showed high dietary protein intake was not associated with a decline in renal function in women with normal renal function during an 11-year period. However, this study also showed that increasing protein intake was associated with accelerated decline in kidney function in women with preexisting mild renal insufficiency. In these women, an odds ratio of 3.51 was determined for a decrease of at least 15% in estimated eGFR between those in the highest quintile of protein intake (92 g/day) compared to those in the lowest (61 g/day), with an estimated decrease in eGFR of 7.72 mL/min/1.73 m^2 per 10 g increase in protein intake. Low eGFR is defined as <60 mL/min/1.73 m^2, according to the Kidney Disease Outcomes Quality Initiative guidelines (22). In the present study, all participants reported an eGFR >60 mL/min/1.73 m^2 at both weeks 0 and 52. This indicates participants had normal renal function and no adverse effects were observed. Hence, the lack of any observed differential effects between the very-low-carbohydrate and high-carbohydrate diets on eGFR, despite a 40-g/day higher protein intake with the very-low-carbohydrate diet, could possibly be attributable to the absence of any preexisting renal insufficiency in the participants studied. Collectively, these data suggest that the chronic consumption of a very-low-carbohydrate weight loss diet may not adversely affect renal function, at least in a patient population without overt renal decline, beyond which the study results should not be generalized. Whether similar effects would be evident in obese individuals with preexisting impaired renal function, including patients with diabetes and/or renal disease, remains unknown and warrants further investigation.

Although the present study has prospectively examined the effects of very-low-carbohydrate and high-carbohydrate diets on renal function in a randomized controlled trial over the longest duration to date, 12 months may still not be sufficient for any adverse effects on renal function assessed by GFR to be observed. A previous clinical trial demonstrated that protein restriction slowed declines in GFR and renal function compared with normal protein intake in patients with severe renal disease after 18-month follow-up (23). In contrast, another study showed no difference in GFR between individuals with moderate renal disease randomized to consume either a low-protein or usual-protein diet after 3 years (24). In this latter study, it was subsequently estimated that because of the slow overall rate of decline in GFR, a longer follow-up of an additional 3 or more years would have been required to detect a difference in GFR between the treatment groups (25). For these reasons, it could be considered that a follow-up of at least 6 or more years may be required to observe any effects of dietary manipulations on long-term GFR in individuals with mild renal insufficiency. This notion is supported, at least in part, by a prospective cohort study that showed dietary protein intake levels affect GFR in this patient population after 11 years (21). Moreover, it is plausible to suggest that even a longer period would be necessary in individuals with normal renal function.

Obesity is associated with increased systemic arterial pressure, high renal plasma flow, and increased GFR (26,27). It is noteworthy that absolute eGFR (mL/min) decreased with weight loss in both treatment groups, independent of dietary composition in the present study. This finding is consistent with previous studies that also showed reductions in absolute GFR following weight loss, which has been suggested to reflect a favorable reduction in obesity-associated glomerular hyperfiltration (26,28). However, because the number of nephrons does not increase with increasing body fat, in order to assess the

relative efficiency of kidney functioning and response to treatment, GFR should be corrected for body surface area. As indicated here, changes in absolute eGFR were associated with weight loss and the change in body surface area such that when normalized for body surface area, eGFR did not change.

A limitation of the current study is that GFR was only estimated using predictive equations. However, the MDRD equation is widely used as an indirect estimate of renal function and was empirically derived from iothalamate GFR measurements and the results obtained using this equation were consistent with data derived using the Salazar-Corcoran formula, which was developed specifically for use in obese patients and has been validated by comparison with direct measurements of creatinine clearance (14). Nevertheless, without a direct isotopic GFR measurement, the exact effects of the dietary patterns evaluated cannot be determined. Furthermore, this study was limited by a relatively high dropout rate (42%) and small sample size. Participants who completed the study may have represented a group of highly motivated individual participants who achieved substantial weight loss, and this could have potentially biased the observed effects and might limit the generalizability of the findings. Consequently, larger studies are required to better delineate these effects.

CONCLUSIONS

In conclusion, the current data suggest that, in people with abdominal obesity and normal renal function, consumption of a very-low-carbohydrate weight loss diet for 52 weeks does not adversely affect renal function compared with a conventional high-carbohydrate, low-fat diet. However, further longer-term studies need to confirm whether very-low-carbohydrate diets alter kidney function, particularly in people with preexisting renal disease.

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