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Is the very low carbohydrate diet safe for individuals with chronic kidney disease?

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Background: The very low carbohydrate diet (VLCHD) is gaining popularity as a therapy for metabolic syndrome. However, its effect on renal function in patients with comorbid moderate to severe chronic kidney disease (CKD) is currently unclear.

Aim: This study analyses markers of kidney function in patients with metabolic syndrome and stages 3 and 4 CKD who undertook a VLCHD for at least 3 months.

Setting: The study was conducted in a Mid North Coast general practice located in Port Macquarie, NSW, Australia, 2020–2022.

Methods: Clinical data were analysed retrospectively from 18 participants with metabolic syndrome and CKD stages 3 and 4, who were prescribed a VLCHD (< 30 g carbohydrates/day). A linear mixed model was used to analyse markers of metabolic health (glycated haemoglobin (HbA1C), body mass index (BMI), blood pressure (BP), lipid profile (triglycerides and low-density lipoprotein cholesterol) and kidney function (estimated glomerular filtration rate (eGFR), serum creatinine, bicarbonate and urea)).

Results: Strong evidence was found for reduced BMI ($p < 0.001$) and HbA1c ($p < 0.001$), despite reduced diabetic medications in 13/14 participants. Antihypertensive medications were reduced in 6/14 participants with no change in systolic BP. No changes were detected in eGFR or bicarbonate, while creatinine ($p \leq 0.001$) and urea ($p = 0.002$) were reduced. No participants deteriorated to a more advanced stage of CKD; rather an absolute eGFR increase was found in 15/18 participants.

Conclusion: For the first time, the VLCHD was demonstrated to reduce BMI, HbA1c, BP and medication burden in patients with CKD stages 3–4 without evidence of kidney damage.

Contribution: The VLCHD could be a safe and effective therapy to improve metabolic health and consequently reduce cardiovascular disease risk in patients with metabolic syndrome and CKD.

Keywords: low carb diet; obesity; metabolic syndrome; type 2 diabetes; ketogenic diet; chronic kidney disease.

Introduction

The 2022 Australian National Health Survey found that almost two-thirds of adults in New South Wales were overweight or obese.[1] Obesity and its associated complications, namely, type 2 diabetes mellitus (T2DM), chronic kidney disease (CKD) and cardiovascular disease (CVD) represent some of the most significant health burdens in the developed world.[1] In turn, obesity is strongly associated with the development of metabolic syndrome – the clinical cluster of central obesity, hypertension, insulin resistance and atherogenic dyslipidaemia (increased triglycerides, decreased high-density lipoprotein cholesterol (HDL)).[2,3,4] The interplay between metabolic dysfunction and CKD is a vicious cycle, as CKD is associated with increasing insulin resistance and worsening metabolic syndrome, which, in turn, worsens CKD.[5] Cardiovascular disease is the most common cause of morbidity and mortality in CKD.[6] Although medical management of CVD and CKD has significantly improved over recent decades, a dietary intervention that reverses insulin resistance and addresses cardiovascular-kidney-metabolic syndrome[7] holistically is likely to be a cost-effective approach to reducing morbidity and mortality from CVD and kidney disease.

In Australia, diabetic medication prescriptions increased by 24% between 2017–2018 and 2020–2021 to 16.5 million, reflecting the epidemic of obesity and insulin resistance in this country.[8] Those living in inner regional areas of Australia, such as Port Macquarie, the site of this study, are more likely to be of lower relative socioeconomic advantage and overweight or obese than those in major cities (70.4% vs. 61.1%), and almost twice as likely to have CVD.[1] Given the health risks

associated with polypharmacy along with high out-of-pocket costs and access barriers, especially for remote and underprivileged populations, there is benefit in a cost-effective, evidence-based, solution as an alternative to escalating prescription of medications.

The therapeutic effects of a very low carbohydrate diet

Therapeutic carbohydrate reduction (TCR) is widely recognised in the literature as an effective treatment for obesity, T2DM, hypertension and insulin resistance. It is also recognised to facilitate medication deprescription.[9,10,11,12,13,14,15,16,17,18,19,20] Cumulatively, these alterations would be expected to lead to beneficial downstream effects in mitigating the burden of CKD.[21] The positive effects of TCR have been acknowledged by the American Diabetes Association and the American Heart Association as an effective and safe dietary intervention for obesity and T2DM.[2,22]

The therapeutic mechanisms of a very low carbohydrate diet (VLCHD) are strikingly similar to the mechanisms of the sodium-glucose co-transporter-2 inhibitor (SGLT2i), which is now an established treatment for CKD. This suggests that VLCHDs may, likewise, have beneficial renal effects.[23] Emerging evidence has shown that a well-formulated VLCHD (which typically involves a moderate dietary protein intake, rather than the common misperception that the VLCHD necessitates a high protein intake) does not adversely impact kidney function biomarkers and may even be beneficial.[17,24,25,26] Bruci and colleagues[12] (2020) found that VLCHD adherence resulted in an improvement of renal function in 27.7% of participants from an estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m^2 – 89 mL/min/1.73 m^2 to an eGFR $\geq$ 90 mL/min/1.73 m^2. In addition, a retrospective cohort study of 2004 patients by Mitchell and colleagues[14] (2021) found that after 1 year of compliance with a VLCHD, the eGFR of patients with stages 2–3 CKD was either unchanged or improved. Furthermore, a 2021 randomised control trial (RCT) by Zainordin and colleagues[16] demonstrated that, after 12 weeks, the VLCHD was just as safe for patients with diabetic kidney disease as the low protein diet (LPD). However, this study was limited by a short follow-up period, a small population and like the aforementioned studies only included participants with stages 2–3 CKD. The effects of VLCHD in patients with severe CKD (stages 3 and 4) have not yet been examined.

Low protein diets

The use of TCR for patients with CKD and T2DM would represent a paradigm shift from current CKD dietary advice which focusses on dietary protein restriction. The Kidney Disease Outcomes Quality Initiative's (KDOQI) 2020 Stages 3–5 CKD guidelines recommend a protein-restricted diet as low as 0.6 g/kg/day – 0.8 g/kg/day for patients with CKD and T2DM.[27] Recent updates to the Kidney Disease Improving Global Outcomes (KDIGO) CKD dietary guidelines, with or without T2DM, now recommend a protein allowance of 0.8 g/kg/day.[28] However, evidence for the LPD is weak[29,30,31] and potential risks include protein energy wasting and malnourishment.[22,30,32] Evidence supporting protein restriction initially emerged in the 1980s, when Brenner and colleagues,[33] based on animal studies, hypothesised that high protein diets (> 1.5 g/kg/day) lead to glomerular hyperfiltration which may accelerate renal function decline. In response, many practitioners cautioned against the use of VLCHDs in those with CKD because of the perceived high protein content.[27,28,34]

However, a recent Cochrane review found no conclusive evidence to suggest an LPD (0.6 g/kg/day to 0.8 g/kg/day) improves eGFR when compared to a more typical protein intake (>1.0 g/kg/day), and concluded that LPDs have little to no effect on progression to end-stage kidney disease.[35] Furthermore, RCTs used to establish current KDOQI guidelines found LPD to have no effect on eGFR when compared to control groups.[27,36,37] Alternatively, an association between higher dietary protein intake and renal function decline was found by Jhee and colleagues[38]. The group with a protein consumption of 1.7 g/kg/day had an annual mean eGFR decline of 2.34 mL/min/1.73 m^2, compared to 2.01 mL/min/1.73 m^2 in the group with a protein consumption of 0.6 g/kg/day. This study is, however, potentially confounded by recall and reporting biases, as protein intake was measured by food frequency questionnaires.

Concerns regarding VLCHD also relate to the commonly higher consumption of animal proteins, which are thought to exacerbate metabolic acidosis and the accumulation of protein by-products, such as urea.[27] However, the current literature examining VLCHD in mild CKD does not report such changes in bicarbonate or urea.[15] This is yet to be examined in stages 3 and 4 CKD.

Other concerns about VLCHD relate to a perceived increase in CVD risk in patients with CKD because of a higher dietary saturated fat content. However, the VLCHD is variably reported to increase, decrease or not change low-density lipoprotein cholesterol (LDL) markers.[12,16,19,39] There is a growing consensus that LDL-particle and apolipoprotein-B are superior to LDL as markers of CVD risk in adults with CKD.[19,40] Increases in LDL during the VLCHD have been attributed to the formation of larger, less atherogenic lipoprotein molecules.[19,41] Additionally, the VLCHD is reported to improve triglycerides, HDL, total LDL-particles, small LDL-particles and apolipoprotein-B levels in patients with T2DM, suggesting that a higher dietary fat content in the VLCHD does not translate to higher CVD risk.[19,20,42,43]

Aim and objectives

Given the evidence that a VLCHD can help reverse metabolic syndrome and reduce CVD risk, it may also be beneficial for individuals with comorbid CKD. While some evidence exists for the safety of a VLCHD intervention in mild CKD, the impacts of a VLCHD in patients with severe CKD are yet to be explored. A major concern has been the perceived risk of

the VLCHD to kidney function, as theorised by those who endorse an LPD. This study addresses those concerns by analysing kidney biomarkers from individuals with moderate to severe CKD who followed a VLCHD for at least 3 months under close clinical supervision. We hypothesise that there will be no detectable deterioration in kidney function alongside improvements in metabolic syndrome. This research will provide further evidence on the safe recommendation of dietary interventions for individuals with metabolic syndrome and CKD, and whether the VLCHD can be effectively implemented in an inner-regional Australian primary care setting.

Research methods and design

Study design

This is a retrospective cohort study designed to observe longitudinal changes to cardiovascular risk factors, glucose regulation and renal function in a cohort of patients with metabolic syndrome and CKD, undertaking a VLCHD for at least 3 months, by examining clinical data routinely collected at a general practitioner (GP) clinic.

Setting, study population and sampling strategy

De-identified data were extracted from the clinical database at a general practice on the Mid North Coast of Australia between 06 June 2020 and 25 August 2022. The clinic was attended by a GP with a special interest in VLCHDs. Most participants were referred by their primary GP, nephrologists and urologists for weight loss or diabetes management, but some sought this GP independently. Inclusion criteria were: age above 18, a diagnosis of metabolic syndrome (defined by the presence of ≥ 3 of insulin resistance, central obesity, decreased HDL, hypertension or increased triglycerides)[44] and a diagnosis of CKD (defined by an eGFR below 60 mL/min/1.73 m^2). Participants were prescribed a VLCHD and monitored for a minimum of 3 months. Those who had a nephrectomy after commencing a VLCHD were excluded. Kidney function was categorised according to the KDIGO guidelines where stage 3a, stage 3b, stage 4 and stage 5 correspond to an eGFR of 45 mL/min/1.73 m^2 – 59 mL/min/1.73 m^2, 30 mL/min/1.73 m^2 – 44 mL/min/1.73 m^2, 15 mL/min/1.73 m^2 – 29 mL/min/1.73 m^2 and < 15 mL/min/1.73 m^2, respectively.[45]

The very low carbohydrate diet

The VLCHD used in this study involved recommending carbohydrate consumption of ≤ 30 g/day. Participants were given a simple explanation of the rationale for the VLCHD and tips for adherence at their initial consultation. Patients were instructed to plan meals with a protein base, add two above-ground, non-starchy vegetables and add fats until satiated. They were instructed to avoid the consumption of grains, potatoes and sugars. Visual guides were employed to illustrate the carbohydrate content in popular food groups. Patients were also taught to assess food labels and identify those with a total carbohydrate content of less than 5 g net carbohydrates per 100 g. Further videos and meal planners were also provided.

Patients were required to return for follow-up after approximately 2 weeks, and then monthly, extending to 3-monthly as clinically appropriate. During these consultations, patients discussed their personal food diaries, which detailed a written record of all foods consumed and at what time. The GP monitored these diaries and adjusted food choices as needed to help patients meet their target carbohydrate consumption. Once the patients became more confident in identifying suitable foods for the diet, the food diary was no longer necessary. The GP also took anthropometric measurements, reviewed laboratory investigations, titrated medications and monitored for adverse symptoms or other patient concerns.

Patients were forewarned of the potential, transient and natriuresis-related adverse symptoms associated with the new commencement of VLCHDs, such as dehydration, lethargy or constipation, sometimes referred to as the 'keto flu'.[24] Participants were instructed to consume salty broths or otherwise increase salt and fluid intake to ameliorate these symptoms. However, participants with hypertension were instructed only to alter their salt intake if they developed hypotension, headaches or constipation.

Insulin medications were reduced in a timely manner to prevent hypoglycaemia. On commencing the VLCHD, short-acting bolus insulin was ceased, and long-acting basal insulin medication doses were halved. Mixed insulins were either halved or changed to basal insulin and the dose was halved. Participants were then required to monitor blood glucose levels (BGLs) before and 2 h after a meal, aiming to keep BGLs below 10 mmol/L. Insulin medications were reduced again when BGLs were below 10 mmol/L and ceased if the daily dose was 10 units – 20 units. Sulfonylureas were ceased prior to commencing the VLCHD to avoid hypoglycaemia. As per clinical protocol at the time, SGLT2i were also ceased prior to commencing the VLCHD. Although SGLT2i are beneficial for glucose control and cardiovascular and renal protection, the treating physician at the time practised caution against the risk of euglycaemic ketoacidosis when pairing the SGLT2i with VLCHD.[46]

Antihypertensive medications were tapered over the first 2 weeks of the VLCHD to avoid hypotension and subsequent acute kidney injury, especially in those with advanced CKD. These participants initially undertook daily home blood pressure (BP) monitoring until their BP was stable, and were screened for symptoms of orthostatic hypotension during follow-up appointments. Antihypertensive medications were ceased if systolic BP fell below a systolic BP of 110 mmHg.

Data collection

Patient demographics and baseline clinical characteristics were collected during the first consultation, prior to

commencing the VLCHD, and are henceforth referred to as 'baseline' data. The most recent available pre-VLCHD blood pathology results were used as the baseline measurements. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[47] Participants were instructed to complete blood pathology prior to consultations. Because participants determined the location of blood sampling, results were received from various pathology clinics. Height and weight were measured using a Seca 213 Portable Stadiometer and Seca 813 Electronic Flat Scales, respectively. Blood pressure was measured using an automatic Omron BP Monitor. Beta-hydroxybutyrate levels were measured at the GP's discretion, using a Freestyle Optimum Neo.

Data analysis

Analysis was conducted in R-4.0.3.[48] Data were available between 10 and 104 weeks (mean 57 weeks) pre-VLCHD, and between 13 and 102 weeks (mean 54 weeks) post-baseline. Because of data limitations, robust model fitting could only be performed from baseline to 52 weeks for primary outcomes. However, 26 weeks pre-VLCHD (n = 12) and 52 weeks post-baseline data could be modelled for safety outcomes. Plots contain all data, including measurements that lie outside these times. Linear mixed models were fitted using the lme4 package,[49] with a fixed effect for time and an interaction of time with an indicator of post-baseline (for safety outcomes only, to allow for a change in slope at baseline) and a random effect of the patient to account for dependence. Ninety-five per cent confidence intervals were calculated using profile likelihood. P-values were calculated using a likelihood ratio test. No p-value cut-offs were used in line with modern statistical practice.[50]

Primary outcomes included body mass index (BMI), systolic BP, HbA1c, triglycerides and LDL, and safety outcomes included eGFR, serum creatinine, bicarbonate and urea. Assumptions were checked with residual plots and variables were transformed as necessary. Residual plots showed a nonlinear relationship between BMI and weeks on a VLCHD, and a model with log(weeks + 1) was found to meet model assumptions. Primary outcomes were controlled for multiple tests using a Holm–Bonferroni correction, and safety outcomes were not controlled for multiple testing.

Ethical considerations

Ethical clearance to conduct this study was obtained from the University of New South Wales Human Research Ethics Executive Committee (No. HC220323). All participants provided informed written consent for their de-identified data to be included in the study. The data of eligible patients were extracted between 06 June 2020 and 25 August 2022. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Sample

The study cohort comprised 18 participants (13 female and 5 male), aged 47–77 years, mean and standard deviation (s.d.) 67 ± 8 years, whose demographic and clinical characteristics are described in Table 1. Because of the retrospective nature of the study, it was not possible to extract data from all patients for all variables; therefore, the sample number (n) is

TABLE 1: Patient demographic and clinical characteristics at baseline and last visit.

Variable	Baseline				Last visit				n†
	n	%	Mean ± standard deviation	Range	n	%	Mean ± standard deviation	Range	
n	18	-	-	-	-	-	-	-	-
Female gender	13	72.0	-	-	-	-	-	-	-
Age (years)	-	-	67 ± 8	-	-	-	-	-	-
Duration (weeks)	-	-	54 ± 31	13–110	-	-	-	-	-
Obesity	17	-	-	-	12	-	-	-	-
CKD Stage 2	0	0	-	-	3	16.7	-	-	-
CKD Stage 3a	8	44.4	-	-	10	55.6	-	-	-
CKD Stage 3b	5	27.8	-	-	3	16.7	-	-	-
CKD Stage 4	5	27.8	-	-	2	11.1	-	-	-
BMI (kg/m^2)	-	-	39 ± 5	29–47	-	-	34 ± 5	26–43	18
Systolic BP (mmHg)	-	-	146 ± 22	120–203	-	-	132 ± 17	100–170	18
HBA1c (%)	-	-	7.4 ± 1.2	6.1–9.4	-	-	6.4 ± 1.0	5.2–9.1	16
Triglycerides (mmol/L)	-	-	2.1 ± 0.6	1–3.3	-	-	1.7 ± 1.0	1–4	15
LDL (mmol/L)	-	-	2.4 ± 1.0	1.1–3.8	-	-	2.6 ± 1.1	1.1–4.7	13
eGFR (mL/min/1.73 m^2)	-	-	40 ± 12	18–59	-	-	48 ± 14	18–67	18
Creatinine (umol/L)	-	-	141 ± 44	90–250	-	-	121 ± 42	75–225	18
Bicarbonate (mmol/L)	-	-	25 ± 3	19–29	-	-	25 ± 3	19–30	18
Urea (mmol/L)	-	-	11.8 ± 4.7	5–23.6	-	-	10.1 ± 4.7	4.5–22	18

Note: Stage 2 = 60 mL/min/1.73 m^2 – 89 mL/min/1.73 m^2; Stage 3a = 45 mL/min/1.73 m^2 – 59 mL/min/1.73 m^2; Stage 3b = 30 mL/min/1.73 m^2 – 44 mL/min/1.73 m^2; Stage 4 = 15 mL/min/1.73 m^2 – 29 mL/min/1.73 m^2.

n, participant number; CKD, chronic kidney disease; BMI, body mass index; BP, blood pressure; LDL, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin.

†, Because of the retrospective nature of the study, it was not possible to extract all measures for all patients; therefore, the sample size for each variable is shown.

shown for each. Follow-up data were, on average, available for 54 weeks, with a range of 13–110 weeks. Participants were monitored for a mean and s.d. duration of 54 ± 31 weeks, ranging 13–110 weeks, measured as a baseline to last/most recent visit. At the time of the VLCHD prescription, all participants had CKD and either T2DM (n = 16) and/or obesity (n = 17).

Primary outcomes

Plots of the primary outcome measures (BMI, systolic BP, triglycerides, LDL and HbA1C) over time are shown in Figure 1, with statistical analysis in Table 2. There was strong evidence (χ^2_1 = 102.7, $p < 0.001$) that BMI decreased by a mean of 1.365 kg/m2 per week (95% confidence interval [CI]: −1.554 to −1.177) with the log of the number of weeks on the VLCHD. The number of participants classified as obese decreased from 17 to 12. Strong evidence (χ^2_1 = 16.9, $p < 0.001$) was also found for an average decrease per week in HbA1c of 0.027 percentage points (95% CI: −0.038 to −0.015). The other primary outcomes, systolic BP, triglycerides and LDL showed no evidence ($p > 0.1$, Table 2) of a change over time, although it is important to note that this was in the context of an overall decrease in antihypertensive medications.

Safety outcomes

Plots of renal biomarkers (eGFR, creatinine, bicarbonate and urea) over time are shown in Figure 2, with statistical analysis in Table 3. There was no evidence (χ^2_1 = 0.5, p = 0.471) of a change in eGFR from pre-VLCHD to the last visit, nor evidence (χ^2_1 = 1.6, p = 0.456) of a change in bicarbonate. Strong evidence (χ^2_1 = 17.4, $p \leq 0.001$) was found for a reduction in creatinine of 0.207 umol/L (95% CI: −0.849 to 0.434) per week post-baseline, compared to the pre-baseline trend, as well as strong evidence (χ^2_1 = 9.5 p = 0.002) of a reduction in urea of 0.143 mmol/L (95% CI: −0.034 to 0.175) per week post-baseline. The distribution of participants in each CKD staging category at baseline and last visit is presented in Table 1. Three participants improved from stage 3a to stage 2, four participants from stage 3b to stage 3a and three participants from stage 4 to stage 3b or 3a. Importantly, CKD progression to a more advanced stage of disease was not observed in any participant.

Two participants with stage 4 CKD experienced an initial drop in bicarbonate, which was resolved using sodium bicarbonate (840 mg) tablets. When this was later withdrawn, serum bicarbonate levels remained stable. Both participants had previously required bicarbonate supplementation, prior to VLCHD commencement.

Medication changes

Table 4 shows the medication loads of participants at baseline and at 3 months post baseline, detailing the changes that occurred during this time. By the last visit, 28 of the 72-baseline diabetic and antihypertensive medication prescriptions were ceased and a further seven were reduced with no adverse outcomes (Table 4). The number and/or dosage of diabetic medications was reduced in 93% (13/14) of participants taking diabetic medications at baseline. Insulin was ceased in 71% (5/7) of participants, and a further two participants had their doses reduced. Sulfonylurea and SGLT2i were completely ceased at baseline as per standard clinical protocol at the clinic at the time this study was undertaken. Dipeptidyl peptidase-4 inhibitors were ceased in 75% (5/8) of participants. Glucagon-like peptide-1 (GLP-1) agonists were prescribed in eight participants following baseline to assist in weight loss and blood glucose regulation. Most medication deprescriptions occurred within the first 3 months of the VLCHD.

Discussion

This study presents real-world data from a cohort of 18 participants with metabolic syndrome and an eGFR of 15 mL/min/1.73 m^2 – 59 mL/min/1.73 m^2 (stages 3–4 CKD) who adhered to a VLCHD for a minimum of 3 months under the guidance of a treating GP. Our results support the value of prescribing a VLCHD for reducing BMI, regulating blood

TABLE 2: Primary outcomes analysis.

Outcome	Post-baseline trend per week	95% CI	Chi-square	*df*	Raw *p*-value	Adjusted† *p*-value
BMI (kg/m^2; log [week+1])	-1.365	-1.554 to -1.177	102.7	1	< 0.001	< 0.001
Systolic BP (mmHg)	-0.236	-0.444 to 0.016	4.4	1	0.036	0.107
HbA1c (%)	-0.027	-0.038 to -0.015	16.9	1	< 0.001	< 0.001
Triglycerides (mmol/L)	-0.010	-0.022 to 0.002	2.6	1	0.104	0.208
LDL (mmol/L)	0.002	-0.008 to 0.013	0.2	1	0.618	0.618

CI, confidence interval; BMI, body-mass index; BP, blood pressure; HbA1c, glycated haemoglobin; LDL, low-density lipoprotein cholesterol.
†, Holm–Bonferroni corrections were used as the adjustment statistic.

TABLE 3: Safety outcomes analysis.

Outcome	Pre-baseline trend per week	Post-baseline trend per week	Change in trend per week	95% CI	Chi-square	*df*	Raw *p*-value
eGFR (mL/min/1.73 m^2)	0.054	0.126	0.073	-0.126 to 0.272	0.5	1	0.471
Creatinine (umol/L)	-0.198	-0.405	-0.207	-0.849 to 0.434	17.4	1	< 0.001
Bicarbonate (mmol/L)	-0.020	0.022	0.042	-0.059 to 0.141	1.6	1	0.456
Urea (mmol/L)	0.105	-0.038	-0.143	-0.034 to 0.175	9.5	1	0.002

CI, confidence interval; eGFR, estimated glomerular filtration rate.

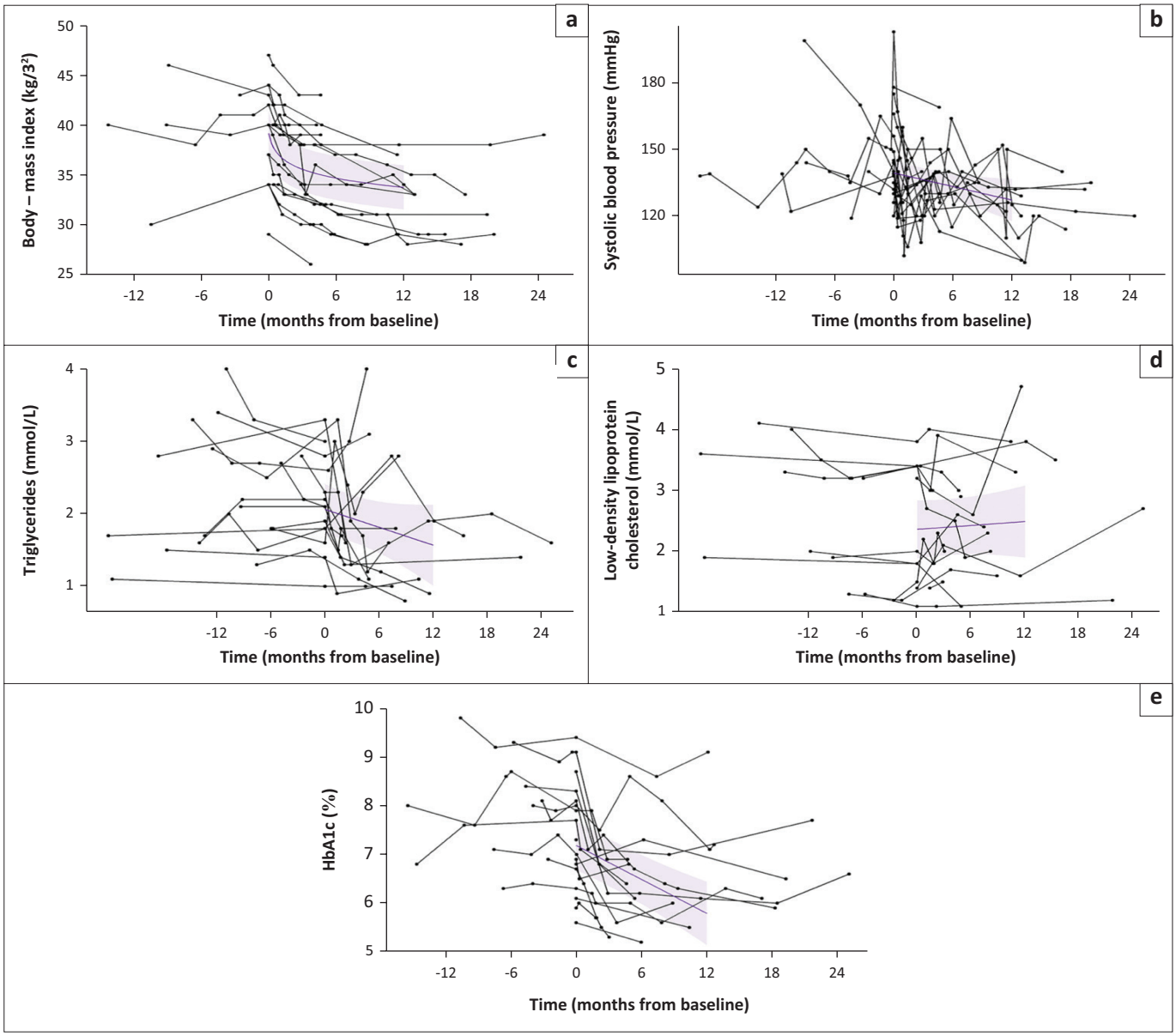

FIGURE 1: Plots of primary outcomes over time (months pre- and post-baseline) overlaid with the modelled trend and 95% pointwise confidence band: (a) body-mass index, (b) blood pressure, (c) triglycerides, (d) low-density lipoprotein cholesterol and (e) HbA1c (%).

glucose and reducing medication burden. Previous studies have provided evidence that a VLCHD is safe for those with mild CKD (stages 2 and 3); however, to our knowledge, the present study is the first to investigate and demonstrate the safety and efficacy of a VLCHD in patients with metabolic syndrome and severe CKD (stages 3 and 4).[12,14]

The major finding of this study was the stabilisation of renal function as measured by eGFR and serum creatinine, as opposed to the progressive decline in renal function that is the natural history of CKD.[51] Not only did renal function stabilise, but the eGFR in 83% (15/18) of participants increased, with 10 participants improving to a less severe CKD stage. Importantly, no participants deteriorated to a more severe CKD stage. While the per-week change in eGFR was not found to be statistically significant, there was a significant downward trend in serum creatinine. Previous studies similarly show improvements in eGFR in those with mild CKD undertaking a VLCHD.[12,13,14] It is important to note that one short-term RCT alternatively reported a decrease in eGFR in a cohort of patients with mild CKD following a VLCHD.[16] The study attributed this finding to the resolution of pathogenic glomerular hyperfiltration, often associated with insulin-resistant obesity and T2DM.[52] The improvements in eGFR found in the present study are unlikely to be attributed to dietary protein-induced hyperfiltration, given the protein content of a VLCHD was only moderate.

This study has also found evidence to address some of the key safety concerns advanced against VLCHDs. Although the VLCHD does not require an increase in specifically animal rather than plant proteins, it is a typical patient practice to increase animal protein intake. There are concerns that the unrestricted intake of animal proteins may exacerbate metabolic acidosis or uraemia in individuals with CKD.[14] However, this study found strong evidence of a reduction in urea after at

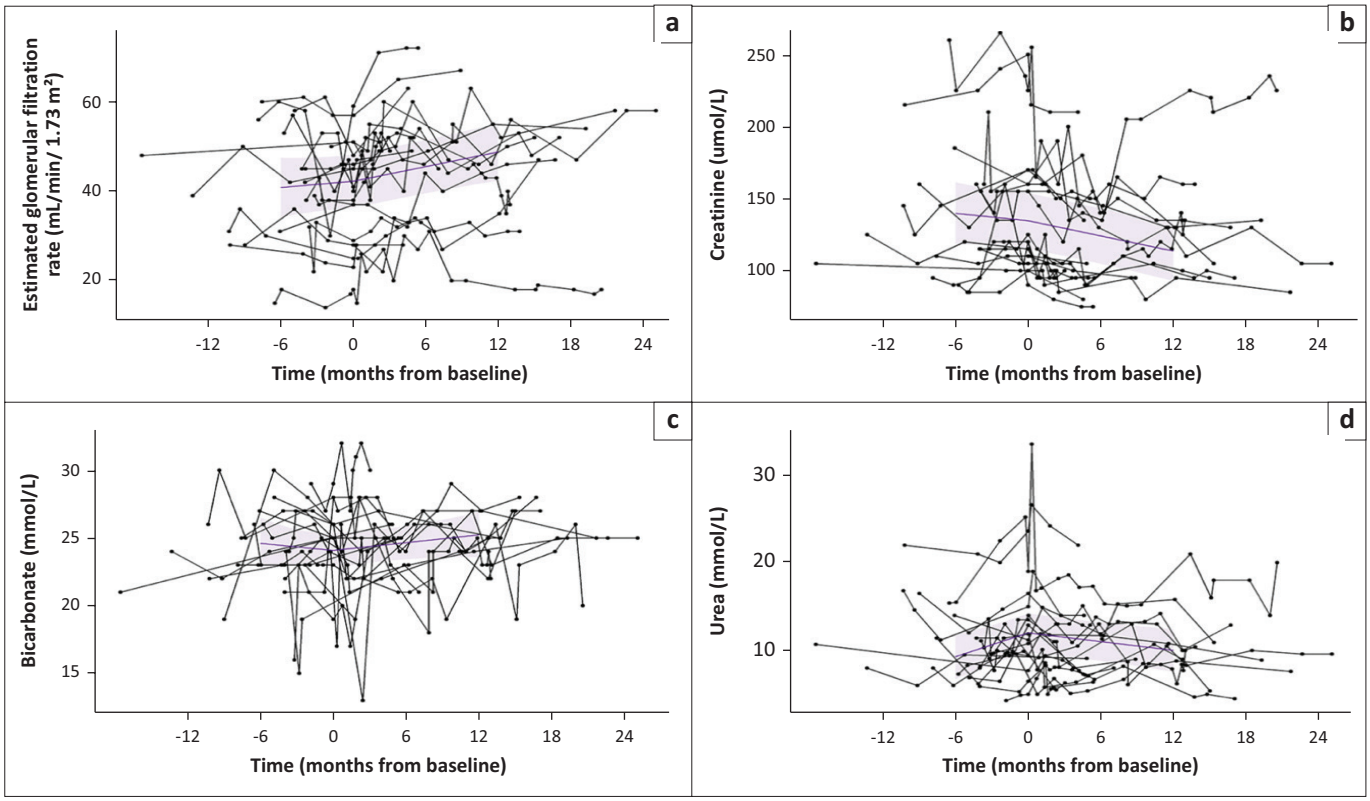

FIGURE 2: Plots of safety outcomes over time (months pre- and post-baseline) overlaid with the modelled trend and 95% pointwise confidence band: (a) estimated glomerular filtration rate, (b) creatinine, (c) bicarbonate and (d) urea.

TABLE 4: Patient pharmacological treatment at baseline and after at least 3 months post-baseline.

Variable	Baseline: Prescribed /18	Changes during the VLCHD at 3 months post-baseline			
		Ceased	Reduced	Unchanged	Started
Insulin	7	5	2	0	0
Sulfonylurea	5	5	0	0	0
SGLT2i	1	1	0	0	0
DPP4i	8	6	0	2	0
Metformin	8	1	0	7	1
GLP-1	3	1	0	2	8
ACE	12	2	1	9	1
CCB	9	3	0	6	0
Other antihypertensives	14	2	4	8	0
Diuretic	5	3	0	2	0

VLCHD, very low carbohydrate diet; SGLT2i, sodium-glucose co-transporter-2 inhibitors; DPP4i, dipeptidyl-peptidase-4 inhibitors; GLP-1, glucagon-like-peptide-1 agonist; ACE, angiotensin-converting enzyme inhibitor; CCB, calcium channel blocker; Other Antihypertensives, other non-diuretic antihypertensives.

least 3 months on the VLCHD. Bicarbonate remained stable in all individuals, except for two patients with stage 4 CKD. These patients had also previously required bicarbonate supplementation prior to the onset of the VLCHD as discussed in the results, as metabolic acidosis often occurs in those with stage 4 CKD.[53] These findings suggest that, although serum bicarbonate should be monitored in severe CKD, it is not a common problem nor contraindicates a VLCHD intervention.

Metabolic outcomes including BMI, systolic BP and HbA1c have consistently improved in studies of patients with T2DM and obesity on a VLCHD.[17,54] In this study of participants with severe CKD, strong evidence was found for a consistent drop in HbA1c after at least 3 months post-baseline. Reductions in blood glucose subsequently allowed most participants to cease their insulin, and 93% (13/14) of participants to reduce their diabetic medications. At the time this study was conducted, SGLT2i were routinely ceased because of the dangers of euglycaemic ketoacidosis; however, current guidelines suggest it may be safe to continue in patients who are not insulinopenic.[46,55]

Strong evidence was also found for a decrease in BMI, as 29% (5/17) of previously obese participants were reclassified as overweight following the VLCHD. This finding supports previous studies and indicates that VLCHDs are an effective tool for weight loss.[16] Similar studies also found a strong correlation between VLCHD and improved BP regulation.[13,17] The improvements in BP seen in this study may be attributed to the natriuretic and diuretic effects of ketosis which alleviates sodium retention, in turn reducing glomerular and systemic BP.[21] This allowed for the deprescription of 6/14 participant's antihypertensive medications. These results indicate that a VLCHD is likely to be of benefit to those with mild to severe CKD, given that hyperglycaemia, obesity and hypertension are drivers of CKD progression and CVD – the most common cause of mortality in this population of patients.[6]

The current study found no evidence of changes in triglycerides or LDL levels in patients with CKD after at least 3 months post-baseline. We were unable to confidently draw conclusions about triglycerides as some blood samples were non-fasting. Studies have previously reported significant

reductions in triglycerides and reversal of dyslipidaemia with VLCHD use.[56] This would be particularly beneficial in insulin-resistant patients with CKD. The lack of a significant change in LDL in this study alludes to the complex relationship between VLCHDs and LDL. A recent meta-analysis by Soto-Mota and colleagues[41] revealed that the relationship between TCR and LDL levels is strongly influenced by BMI. Specifically, increases in LDL were observed for individuals with BMI < 25, no change was seen between BMI 25 and 35, and decreases were seen in individuals with BMI > 35. In our cohort, 17 of the 18 patients were obese, which may explain why no significant rise in LDL was observed.

As demonstrated in Figure 1 and Figure 2, our cohort of 18 participants began to experience the positive effects of a VLCHD within the first 3 months. However, because of the retrospective nature of the study, it was not possible to ensure all outcome data were collected precisely at the 3-month mark. Despite this limitation, medication data were available, showing most deprescription occurred rapidly after commencing the VLCHD. These findings suggest that the rapid beneficial effects of the VLCHD encourage adherence, especially among individuals who are able to discontinue insulin therapy.

The overall safety of a VLCHD is reliant on responsible clinical dietary management, biochemical monitoring, follow-up and prompt medication alteration. Adverse events may arise from clinicians refraining from re-evaluating diabetic and antihypertensive medications as BP and T2DM rapidly improve, risking the development of hypotension and hypoglycaemia.

Strengths and limitations

The GP clinic where this study was conducted focused on treating metabolic disease, allowing the clinician to closely monitor patients with severe CKD and facilitate the implementation of the VLCHD in this new patient group – a group that may have otherwise not been given the opportunity to undertake a therapeutic diet such as the VLCHD. As a result, a key strength of this study was the availability of longitudinal data relating to multiple kidney function outcomes on a wide range of participants with mild, moderate and severe CKD. The study was therefore able to demonstrate the positive effects of the VLCHD across the domains of BMI, regulation of BGL and reduction in medication burden and determine kidney health during the diet using a range of measures. Additionally, this study was conducted within a community setting, with limited resources, suggesting that this treatment could be highly cost-effective, scalable and suitable for a range of regional and rural communities. Given this study has shown the safety of the VLCHD in those with severe CKD, it provides practical instruction to other physicians as to how to manage the VLCHD therapeutic intervention.

Similar studies in the future could improve on this study in several ways. The retrospective nature of the study limited the availability of a standardised consultation visit timeframes, so biochemical markers were not always available in the same units and at the same time points. Pathology samples were also not always collected after overnight fasting. Albuminuria and proteinuria are important indicators of renal dysfunction used routinely to monitor CKD severity.[4] Unfortunately, because of discrepancies in pathology requests for different markers (protein creatinine ratio or albumin creatinine ratio), there was insufficient data in this study to allow statistical analysis of these metrics. Very low carbohydrate diet adherence was not directly measured routinely as blood ketones were measured at the clinician's discretion. Very low carbohydrate adherence may remain a challenge; however, with high-quality patient education and frequent follow-up, adherence was able to be optimised in this study. Glucagon-like peptide-1 agonists were being taken by 10 patients during the diet, which would have been appropriate to include as a confounding variable. However, this was not possible because of the small sample size, variation in start and end dates and overall duration of medication adherence during the VLCHD. The kidney function was calculated by the EPI-CKD equation. This formula is dependent on serum creatinine which may be impacted by dietary protein, dietary meat intake, muscle mass and ketosis.[57,58] Cystatin C and creatinine clearance, unaffected by these variables, may be a preferable measure of renal function in future studies.[58] Isotopic GFR is not used in routine clinical practice but would be the most accurate measure.[57] Reduction in lean muscle mass and therefore serum creatinine is a confounder in these results that will need to be explored in future studies using more sensitive markers of GFR.

Conclusion

Our study is the first to show that a VLCHD is likely to be a safe and effective therapeutic intervention in the population of people with metabolic syndrome and severe CKD (stages 3–4). This study found that a VLCHD can improve BP, HbA1c and BMI and reduce medication burden, without causing renal damage, as measured by eGFR, serum creatinine, bicarbonate and urea. On the contrary, eGFR improved in 15 out of 18 participants. It was also demonstrated that this dietary intervention could be conducted in the community with standard GP clinic resources. The value of this study establishes the basis for future RCTs, so that the appropriate diet may be recommended to patients with metabolic syndrome and CKD. It would also be important to qualitatively assess how adhering to a VLCHD may impact the quality of life, to capture the broader impacts of this diet.

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Competing interests

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Authors' contributions

P.E.F., E.C.S. and M.V. devised the project and the main conceptual ideas. P.E.F. contributed to the treatment of the participants. E.C.S. and G.P. formulated the methodology. Formal analysis was conducted by G.P. and B.S.C. Data curation was managed by P.E.F., B.S.C. and B.J.C. The original draft preparation was performed by B.S.C., P.E.F. and B.J.C. B.S.C., P.E.F. and E.C.S. assisted with the reviewing and editing process. P.E.F., E.C.S. and M.V. supervised this project. The project administrators were E.C.S. and P.E.F. All authors have read and agreed to the published version of the article.

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Data availability

Data may be obtained from a third party and are not publicly available. The anonymised (de-identified participant data) are on an Excel Spreadsheet held by the corresponding author, P.E.F.

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