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CKJ REVIEW

The effect of a ketogenic diet on weight loss in CKD: a randomized controlled trial in obese stage G1–3a CKD patients

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ABSTRACT

This study describes a multicentre randomized controlled trial comparing the effects of a ketogenic diet with a low-energy standard diet containing 0.8 g/kg/day on weight loss and metabolic alterations in adult patients with mild-to-moderate non-diabetic chronic kidney disease (CKD) and mild-to-severe obesity. The study is being conducted to understand the impact of the ketogenic diet on weight loss in these patients, as the existing evidence on the ketogenic diet's effect in CKD patients is limited and inconclusive. The study will enrol mild-to moderate adult CKD patients (Stages G1–3a) with albumin to creatinine ratio ≥200 mg/g, without diabetes, with obesity (body mass index ≥30 kg/m^2), and stable body weight and estimated glomerular filtration rate from at least 3 months. The primary outcome will be weight loss at 6 months, and secondary outcomes will include adherence to prescribed dietary regimens, body composition changes, changes in standardized blood pressure measurements, metabolic parameters, lipid profile, liver profile, mineral bone disease biomarkers, and changes in renal function and albuminuria. The findings of this study will contribute to a better understanding of the potential benefits and risks of the ketogenic diet in CKD patients with obesity. The results will help guide future research on the ketogenic diet and renal health.

Keywords: CKD, dietary proteins, ketogenic diet, low-carbohydrate diet, obesity

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INTRODUCTION

Obesity and chronic kidney disease (CKD) are major global public health concerns. Individuals with obesity are at an increased risk of developing CKD and are at a higher risk for CKD progression [1]. Metabolic disorders such as insulin resistance, dyslipidemia and hypertension are hallmarks of obesity and CKD.

The ketogenic diet, a high-fat, very low-carbohydrate and moderately high-protein (high for CKD) regimen, has gained popularity for its potential to promote weight loss and improve metabolic health. However, its potential impact on body weight in CKD patients is poorly understood, and concerns about renal safety have been raised [2].

The ketogenic diet has become increasingly popular in recent years. With 25.4 million unique searches, the keto diet was the most Googled diet in the USA in 2020 (quoted by McGaugh [3]). The popularity of this diet depends on the fact that it does not restrict calorie intake and allows a higher weight loss in the short term compared with low-calorie diets [4].

Existing evidence on the efficacy of the ketogenic diet in CKD is limited, with the inclusion of heterogeneous patient populations and varied interventions and inconclusive results. In a prospective study of 92 mildly-to-moderately obese patients with stage 1–2 CKD [5] participants received a very low-calorie (450–800 kcal) ketogenic diet (20 g carbohydrates, 1–1.5 g protein/kg, 15–30 g fat) for 3 months. Weight loss of around 20% was observed, along with improved metabolic parameters and no change in renal function, except for a significant increase in estimated glomerular filtration rate (eGFR) in stage 2 CKD patients, attributed to the glomerular haemodynamic effects of high dietary proteins. A randomized trial in 30 patients with type 2 diabetes, mild CKD (GFR 60–70 mL/min/1.73 m^2) and mild obesity (BMI 30 kg/m^2) a very low-carbohydrate (<20 g), moderate low-protein (44 g) diet reduced HbA1c, fasting glucose, insulin dose and weight by <10%, with no observed worsening of serum creatinine as compared with a normal-carbohydrate (90 g), low-protein (29 g) diet [6]. Only three registered ongoing trials exist [7–9].

In light of the limited and inconclusive evidence on the effects of the ketogenic diet in CKD patients, more research is needed to elucidate its potential benefits and risks.

This multicentre randomized controlled trial addresses this knowledge gap by examining the impact of a ketogenic diet compared with a low-energy diet containing 0.8 g of protein/kg/day on weight loss and metabolic alterations in adult patients with mild-to-moderate non-diabetic CKD and moderate-to-severe obesity.

The findings of this study will contribute to a better understanding of the potential benefits and risks of the ketogenic diet in CKD patients with obesity. These results will help guide future research on the ketogenic diet and renal health.

INTERVENTIONS

This study is a pilot, explanatory, randomized, controlled trial enrolling mild-to-moderate adult CKD patients (Stages G1–3a) with albumin to creatinine ratio ≥200 mg/g, without diabetes, with obesity [body mass index (BMI) ≥30 kg/m^2], and stable body weight and eGFR from at least 3 months. Kidney transplant patients and those with active neoplastic or systemic diseases or steroids will be excluded. Furthermore, patients must have been not on a ketogenic or hypocaloric diet during the previous 6 months and should be free of eating or psychiatric disorders.

Study diets

Participants will be randomly assigned to a ketogenic diet (usual energy intake: ~fat 70%, protein 25%, carbohydrates 5%) or a control diet containing 0.8 g/kg/day of proteins (low energy intake: ~fat 25%, carbohydrates 60%) for 6 months. No caloric restriction will be applied to patients of the active arm. For patients in the control arm, the caloric intake will be profiled according to a calculator that gives information on the calories needed for gradual weight loss [10] (https://www.healthline.com/nutrition/how-many-calories-per-day). A standard, minimum physical activity will be prescribed to all patients (at least 150 min per week of moderate-intensity, 75 min per week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity; preferably, aerobic activity should be spread throughout the week; (https://health.gov/sites/default/files/2019-10/PAG_ExecutiveSummary.pdf).

Patients will be monitored monthly for metabolic acidosis (HCO_3 <22 mmol/L) and hyperkalemia (serum K ≥5.5 mEq/L). The eventual onset of either complication will prompt intervention along with current guidelines and recommendations.

STUDY FLOW AND TRIAL IMPLEMENTATION

During the run-in period, lasting 3 months, the individual dietary intake will be measured on at least two occasions, at least 2 weeks apart. During the run-in period, established therapies (KDIGO guidelines [11–13]) for CKD will be optimized. Patients on renin–angiotensin system (RAS) inhibitors will maintain this treatment and those off this treatment will start renin–angiotensin–aldosterone system inhibitors. Dapaglifozin, 10 mg/day, will be then introduced. While maintaining their customary diet, during the run-in period, patients in both study arms will be educated on complying with the prescribed dietary regimen (ketogenic vs control diet) during this period. At least four educational sessions will be organized, and booklets on the dietary constituents of the diets being compared will be distributed to participants. The two dietary regimens will be maintained for 6 months. During the trial, monthly encounters with nutritionists of participating centres and telephone and/or e-mail or WhatsApp contacts will be warranted. After the end of the trial, patients will be followed up for an additional 6 months to monitor body weight and metabolic parameters post-intervention. The last visit and the last set of measurements will be fixed 12 months after the trial start.

OUTCOMES

The primary outcome will be the weight loss at 6 months. Secondary outcomes will include body weight loss at 12 months, adherence to prescribed dietary regimens (ketogenic and control diet), palatability of the dietary regimens, proportional energy intake by the main nutrients (carbohydrates, proteins, lipids), changes in body composition (fluid volumes, fat mass, lean mass—measured by the Body Composition Monitor or another validated multifrequency bioimpedance instrument) and muscle strength (the sit-to-stand test), changes in standardized blood pressure measurements (KDIGO 2021 guideline [11]), antihypertensive drugs, metabolic parameters (insulin resistance as measured by HOMA index [14]), lipid profile, liver profile, mineral bone disease biomarkers [serum calcium, phosphate and parathyroid hormone (PTH), bicarbonate and C-reactive protein, changes in renal function (eGFR as estimated by the Pottel's

cystatin equation [15]) and renal damage (albumin to creatinine ratio), and changes in the perceived quality of life as assessed by the Kidney Disease Quality of Life Short Form (KDQOL®, short form, Italian version) (https://www.rand.org/pubs/papers/P7928z2.html).

MEASURES

The main outcome of this study is weight loss. Weight will be accurately measured according to a standardized protocol (see Supplementary data). Routine clinical laboratory tests include serum creatinine, Cystatin, glucose, total and low-density lipoprotein and high-density lipoprotein cholesterol, triglycerides, urate, insulin, phosphate, calcium, sodium, potassium, albumin, high-sensitivity C-reactive protein, PTH and fibroblast growth factor 23, urine protein to creatinine ratio and urine albumin/creatine ratio in early morning urine, 24-h proteinuria and albuminuria, phosphaturia, urea, creatinine, sodium and potassium. All these measurements will be done at the end of the run-in period (last week), at baseline (the day before the intervention starts), and after 6 and 12 months. Measurements will be performed in certified pathology units serving the centres participating in this study.

Nutritional assessment will be done by standard physical measurements (height, weight and BMI, waist circumference and waist to hip ratio), and the quality of life by the KDQOL®, short form. Muscle strength will be estimated by the sit-to-stand test (and, possibly, hand dynamometry). Careful dietary interviews about the palatability and pleasantness of the diets being compared and periodic food diaries will be administered during the run-in, at baseline and at monthly intervals thereafter.

Metabolomics and microbiota studies parallel to the trial are foreseeable if interested investigators warrant the techniques needed for corollary projects.

STUDY POWER

Based on a power calculation assuming a 25% attrition rate, a sample size of 84 participants (42 in each group) will be required to detect a difference of 3 kg in weight loss between the two groups at 6 months, assuming a standard deviation of 4 kg and a power of 80%.

DATA ANALYSIS

Data will be analysed using the intention-to-treat principle. Descriptive statistics will be used to summarize participant characteristics. Continuous variables will be compared using the independent t-test or Mann–Whitney U test, depending on the distribution of the data. Categorical variables will be compared using the chi-squared test or Fisher's exact test. A P-value of $<.05$ will be considered statistically significant.

ETHICS AND DISSEMINATION

This study will be conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of participating centres. Informed consent will be obtained from all participants before enrollment. The results of this study will be disseminated through peer-reviewed publications and conference presentations.

DISCUSSION

Herein we describe the design of a randomized controlled trial comparing the effects of a ketogenic diet versus a low-energy diet containing 0.8 g/kg/day on weight loss and metabolic alterations in adult patients with mild-to-moderate non-diabetic CKD and mild-to-moderate obesity. The rationale for the study is based on the growing interest in the potential benefits of ketogenic diets for weight loss and metabolic health, and the paucity of evidence regarding their impact on renal function in CKD patients.

The dramatic increase in obesity worldwide and its role in engendering CKD and accelerating renal function loss in CKD patients [16] remains challenging. There is an urgent need to test the effectiveness and safety of several widely used weight-loss diets. A Cochrane meta-analysis in 2017 identified only two trials testing nutritional interventions in obese CKD patients, globally enrolling 33 patients randomized to a low-calorie diet and 23 to a control diet [17].

A low-carbohydrate diet (ketogenic diet) is a dietary approach that restricts carbohydrate intake and promotes higher consumption of fat and protein. Carbohydrates are the body's preferred energy source, but when restricted, it turns instead to fat stores for fuel. This can lead to a reduction in body weight and body fat. A meta-analysis of randomized controlled trials found that low-carbohydrate diets were more effective for weight loss than low-fat diets in the short term [18]. Furthermore, a low-carbohydrate diet may improve control of hyperglycemia in diabetics [19] and hypertension control, triglyceride levels and high-density lipoprotein cholesterol levels in diabetic and non-diabetic obese patients. These improvements may reduce risk factors for heart disease and stroke [20], which are major complications in CKD patients.

Concerns about ketogenic diets in CKD have been expressed. In theory, high protein intake may cause glomerular hypertension and hyperfiltration, kidney damage, proteinuria and long-term worsening of renal function [21]. Additionally, the high content of lipids, animal proteins, phosphate and acids in the ketogenic diet could exacerbate several metabolic derangements typical of CKD, such as hyperlipidemia, hyperphosphatemia, metabolic acidosis with concurrent hyperkalemia, and increased release of uraemic toxins by gut microbiota [21]. On the other hand, higher protein intake could improve impaired bone health in CKD patients, and ketosis has been hypothesized to inhibit cyst growth in autosomal dominant polycystic kidney disease [22]. Population-based studies have shown that higher protein intake is associated with increased mortality in individuals with reduced renal function, whereas lower protein intake is associated with higher mortality in individuals with normal kidney function [23]. These theoretical concerns are negated by trial evidence. In a meta-analysis of randomized trials with a duration of up to 2 years, no adverse renal effects of low-carbohydrate diets compared with control diets of higher carbohydrate content were registered [24]. Another meta-analysis of trials that enrolled diabetic patients with normal eGFR suggested that neither the eGFR nor albuminuria were affected by this diet intervention [25]. Small, exploratory studies in CKD patients confirm the safety of the low-carbohydrate diet in CKD [5, 6]. Furthermore, in the landmark trial that compared a low-carbohydrate, ketogenic diet with a low-fat and Mediterranean diet in 322 moderately obese subjects and that included patients with mild-to-moderate CKD (serum creatinine <2 mg/dL) over a 2-year follow-up, no safety concerns emerged in the CKD population, or adverse effects on kidney function

or kidney damage. The present multicentre study will enroll patients with normal renal function and albuminuria (stage G1–2) and stage G3a patients showing an eGFR ranging from 60 to 45 mL/min/1.73 m^2. Metabolic complications are absent or uncommon when the eGFR is normal or mildly to moderately reduced [26].

During the run-in period, we contemplate the optimization of CKD therapies along with recommendations by KDIGO guidelines. Sodium–glucose cotransporter 2 inhibitors (SGLT2-i) are increasingly used in overweight and obese CKD people, and due to their established efficacy, these drugs are now recommended in diabetic and non-diabetic CKD patients. For this reason, starting from the run-in period, patients in both study arms will start therapy with dapagliflozin, the only available SGLT2-i with a reimbursed indication for albuminuric CKD in Italy. The inclusion of dapagliflozin as a background treatment in the trial will ensure the maximization of the benefits of established treatments in both study arms and will prevent the potentially unbalancing effect (trial contamination) of this or other SGLT2-i inhibitors deriving from the unplanned prescription of these drugs by doctors taking care of the patients enrolled in the trial. Due to the risk of keto-acidosis, SGLT2-I are discouraged in diabetic patients on low-carbohydrate diets. For this reason, diabetic patients will be excluded from the trial.

Some limitations of this trial should be acknowledged. First, the primary endpoint of the trial is weight loss at 6 months, a short treatment period. However, the interventions (low-carbohydrate and control diet) will be continued up to 1 year to assess the long-term impact of the diets on renal function and other secondary endpoints. Second, the study may face challenges in recruitment due to potential concerns from patients and healthcare providers about the safety of the ketogenic diet in CKD patients. Third, there may be difficulties in achieving and maintaining high levels of adherence to the prescribed diets, which could affect the validity of the findings.

Despite these limitations, the results of this trial will provide insights into the potential benefits and risks of the ketogenic diet in CKD patients with obesity. These findings will guide future research in this area. In particular, the study may pave the way for larger, longer-term trials to explore further the effects of the ketogenic diet and other dietary interventions on renal function and overall health in CKD patients.

In conclusion, this randomized controlled trial will provide information about the feasibility, effects and safety of a ketogenic diet versus a usual diet on weight loss and metabolic alterations in obese CKD patients. This study may inform larger, long-term studies testing the same diets in CKD patients.

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

CONFLICT OF INTEREST STATEMENT

C.Z. and F.M. are members of the *CKJ* editorial board.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

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