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Low carbohydrate diet for diabetic cardiomyopathy: Protocol for a randomised controlled trial

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Background: Insulin resistance (IR) and type 2 diabetes (T2DM) promote myocardial dysfunction in the absence of traditional cardiovascular risk factors such as hypertension or coronary heart disease. Termed diabetic cardiomyopathy (DMCM), this type of cardiomyopathy often evolves to heart failure (HF), therefore worsening outcomes for people living with T2DM. Low-fat diets (LF) have been recommended for patients with cardiovascular disease but have provided limited symptom relief.

Aim: The aim of this research is to examine the effect of a low-carbohydrate (LC) diet compared with usual care (UC) in patients with DMCM. This study hypothesises that the LC diet will improve symptoms of HF and quality of life (QoL) in patients with DMCM.

Setting: For this 16-week randomised controlled trial 80 adult patients (> 18 years of age) with T2DM (HbA1c ≥ 6.5) or IR (triglyceride glucose index value [TyG] > 4.49) and HF from an outpatient HF clinic in Victoria, Australia were recruited.

Methods: Participants will be randomised to a LC or a LF diet (UC) group. The primary outcome is a composite endpoint of changes in New York Heart Association (NYHA) class, hospital admissions, thirst distress and QoL. The secondary endpoint is a 2% change in HbA1c from baseline. Outcomes will be assessed at baseline, week 6 and week 16.

Results: This article describes a protocol for a radomised controlled trial (RCT). The results of this trial will be published at the completion of the study.

Conclusion: The results from this trial will provide an insight into the future dietary management of DMCM for both patients and healthcare practitioners.

Keywords: low-carbohydrate diet; therapeutic carbohydrate restriction; heart failure; type 2 diabetes mellitus; insulin resistance; quality of life.

Introduction

Cardiovascular disease (CVD) is highly prevalent in patients living with type 2 diabetes (T2DM). There is a strong association between hyperglycaemia, poor blood glucose control and the development of heart failure (HF). Literature suggests that for each 1% increase in mean glycaemic levels, as referenced by HbA1c (glycosylated haemoglobin), there is an 8% increased risk of HF.[1] Equally, insulin resistance (IR) is a strong predictor of HF and was identified as one of the main drivers in the pathogenesis of HF and diabetic cardiomyopathy (DMCM).[2,3,4] In patients with diabetes or IR the cardiac energy metabolism is significantly altered. Toxic lipid and glucose intermediates trigger several adverse signalling pathways, mitochondrial dysfunction and tissue inflammation.[5] This subsequently induces the typical features of diabetic and/or IR cardiomyopathy, which are left ventricular hypertrophy and diastolic dysfunction.[6] Heart failure and T2DM have a synergistic effect, which is demonstrated in increased symptom burden, hospital admissions and mortality in affected patients.[5]

The predominant symptoms of HF are dyspnoea, fatigue and other manifestations of poor cardiac output and congestion. Thirst is a common feature among patients living with HF. It can be exacerbated by the clinical management and self-care directed at alleviating the symptoms of systemic congestion.[7,8]

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Diet has been identified as a modifiable risk factor and a cornerstone for the treatment of both diabetes and HF.[9] Standard care as outlined in the existing global guidelines for the primary and secondary prevention of CVD, includes restrictions in calories, salt, saturated and total fat and focuses on increasing the intake of vegetables, fruit, whole grains as well as foods rich in mono- and poly-unsaturated fats.[10,11,12]

A separate body of evidence suggests that therapeutic carbohydrate restriction may offer benefits over low-fat (LF) diets particularly in patients with underlying glucose metabolism disorders such as diabetes.[13]

Multiple systematic reviews and meta-analyses indicate that low-carbohydrate (LC) diets are an important addition to existing heart healthy dietary patterns and are efficacious in improving glycaemic control and cardiovascular health in patients living with diabetes.[14,15,16,17] Generally, LC diets reduce overall dietary carbohydrate (CHO) intake to less than 130 g/day. Depending on the style (e.g. Atkins, Paleo) or goal (weight loss, diabetes remission) of the LC diet, very LC ketogenic diets may recommend less than 30 g of dietary CHO per day.[18,19] Specifically, LC diets (compared with LF diets) have demonstrated greater reductions in glycated haemoglobin (HbA1c) and sustained improvements in diabetic dyslipidaemia as defined by elevated triglyceride and small dense low density lipoprotein (LDL) particles and decreased high density lipoprotein (HDL).[14,16,20]

However, research investigating the effects of a LC diet in patients with DMCM or HF is scarce. In one 5-week crossover study, Von Bibra et al.[21] compare the effects of a LC and a LF diet on diastolic cardiac function and markers of IR. While weight loss was similar in the LC and the LF groups, mean systolic blood pressure, fasting and postprandial triglyceride and insulin levels only improved significantly on the LC diet ($p < 0.05$). In addition, the authors described a significant improvement in maximal exercise capacity (2 ± 7-watt, $p < 0.05$) and markers of IR (Homeostatic Model Assessment for IR [HOMA-IR]) in the LC but not in the LF diet group (LC −0.9 ± 2.4, $p < 0.05$; LF −0.1 ± 1.4, $p > 0.05$). On the other hand, data from animal studies have repeatedly demonstrated that LC diets improve cardiac remodelling and halt HF development.[22,23,24] This success appears to be in part because of diet-induced ketogenesis and the protective role of ketone bodies against oxidative stress and myocardial damage.[25] The enhanced fatty acid metabolism driven by the LC diet and the dietary CHO restriction itself has also shown to prevent and reverse HF in mice.[26] As a result of the scarcity of evidence regarding an optimal dietary pattern for patients with DMCM, the authors propose to undertake a randomised controlled trial (RCT) to determine the effects of a LC diet in patients with DMCM.

The study's aims and hypothesis

The specific aims for the RCT are as follows:

- To evaluate whether dietary carbohydrate restriction compared with conventional dietary advice recommended for heart health, improves HF symptoms such as shortness of breath and exercise tolerance in patients with DMCM.
- To investigate whether thirst and thirst distress is reduced by dietary carbohydrate restriction in patients with DMCM.
- To determine whether a LC diet improves quality of life (QoL) in patients with DMCM.

The authors hypothesise that a LC diet would improve HF symptoms through two main pathways: (1) IR is known to be a major culprit for the progression of HF.[27] Dietary CHO restriction reduces blood glucose and insulin levels, hence manages IR. It is plausible that a LC diet improves myocardial function and energy supply in the failing heart. (2) Reducing blood glucose and insulin levels through a LC diet promotes diuresis and sodium excretion by decreasing the expression of sodium glucose transporter 2 (SGLT2) receptors in the renal tubules.[28] Consequently, this may lower blood pressure levels and alleviate oedema in patients living with DMCM. It is further hypothesised that these effects of the LC diet will have a flow-on effect on the well-being and QoL of patients with DMCM.

Ethical considerations

Ethical approval was sought and granted from the study hospital and the University Human Research Ethics Committee (ethical approval no. ND 69645/2020).

All procedures performed in this study are in accordance with the ethical standards of the National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Methods

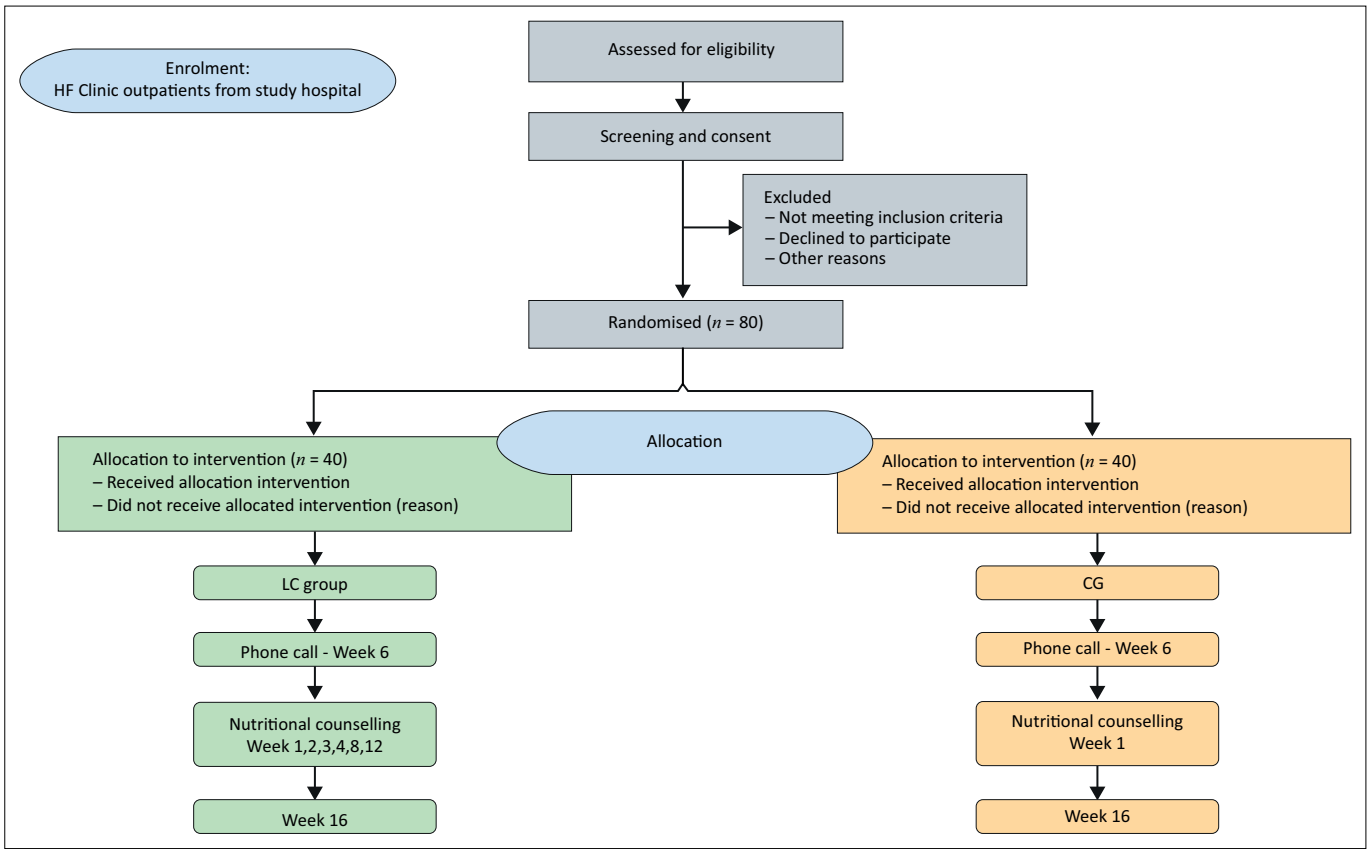
Study design and setting

The authors propose a RCT design to compare a LC diet intervention with standard care (LF diet [usual care, UC]) for patients with DMCM. The study is registered with the Australian and New Zealand Clinical Trial Registry (ANZCTR): ACTRN12620001278921p.

Adult participants are currently recruited from the outpatient's HF clinic of a single centre quaternary metropolitan hospital in Victoria, Australia.

Statistical power and justification of sample size

In this RCT, the authors aimed to recruit a total of 80 participants (40 participants in UC and 40 in the LC intervention group) (Figure 1). This confers 80% power to detect a difference in HF symptoms assessed as a composite endpoint between the two groups of 30%, when the proportion of participants who improve in the control group is assumed



HF, heart failure; CG, control group.

FIGURE 1: Consort chart for the proposed RCT.

to be 20% (significance level 5%, two-sided test). This proposed effect size is drawn from that observed by Philipson et al.[29] with a less intensive intervention. They found that their intervention group had a 50% improvement in the primary endpoint compared with the control group with a 20% improvement in the primary endpoint.[29]

Recruitment and screening

Convenience sampling is used to recruit participants from an outpatient HF clinic. Weekly lists of patients attending the HF clinic will be screened for potential participants. As a result of the ongoing coronavirus disease 2019 (COVID-19) restrictions participants will be invited by phone call. Eligibility criteria were developed to identify patients with either T2DM or IR and HF. Insulin resistance was determined by the triglyceride and glucose index (TyG). The TyG is a simple, cost effective and reliable tool to identify IR in an individual.[30] It is defined as TyG = Ln (fasting triglyceride [mg/dL] × fasting glucose [mg/dL]/2).[31] The cutoff for IR is placed at the TyG index of 4.49 with a sensitivity of 82.6% and specificity of 82.1% (area under curve [AUC] = 0.889, 95% confidence interval [CI]: 0.854–0.924).[32] Patients currently taking SGLT2 inhibitors (SGLT2i) will be excluded as the addition of a LC diet is associated with an increased risk of diabetic ketoacidosis (DKA).[18] Informed consent will be obtained before commencement of the study. Table 1 depicts the full inclusion and exclusion criteria.

TABLE 1: Study inclusion and exclusion criteria.

Inclusion	Exclusion
Age: > 18 years	Type 1 diabetes
HF diagnosis based on echocardiography and Boston criteria	T2DM requiring insulin
Diagnosis of T2DM (HbA1c ≥ 6.5%)	Currently taking SGLT-2 inhibitors
Not diagnosed with T2DM but diagnosed with IR as defined by a triglyceride and glucose index (TyG) value of > 4.49	Unable to give informed consent
Ability to speak and understand sufficient English to consent	Cardiac cachexia†
Access to an electronic device with internet connection	Chronic kidney disease (eGFR < 50 mL/min/1.73 m²)
-	Active cancer treatment
-	Substance abuse disorder (incl. alcohol)

IR, insulin resistance; T2DM, type 2 diabetes; SGLT-2, sodium glucose transporter 2; eGFR, estimated glomerular filtration rate.

†, Cardiac cachexia is defined by an unintentional non-oedematous weight loss of > 5% over at least 6 months.

Randomisation and blinding

The stratified, random assignment of participants into two similar study groups not only ensures that differences in outcomes are ascribed to the intervention but also that each participant has an equal chance of receiving the intervention. The sample will be divided into three strata based on gender, participants diagnosed with T2DM and participants identified to be IR. Following this, participants will be randomised into one of two groups, the LC or UG, on a 1:1 ratio. Randomisation will be undertaken by a member of the research team using a random allocation software, https://randomizer.org. Study participants and the research team

will not be blinded for this pilot RCT because of the nature of the dietary intervention.

Procedures

Intervention group: Low-carbohydrate diet

Participants are coached by a member of the research team, to follow a LC diet as defined by an intake of less than 130 g of carbohydrate per day.[18] To achieve this, the participants will be instructed to consume a variety of above the ground and green leafy vegetables and small amounts of fruit, starchy vegetables and legumes and nuts/seeds are permitted. Participants are encouraged to eat freely animal and plant proteins such as meat, chicken, fish, eggs, unsweetened dairy products and tofu or tempeh. Participants will be coached to avoid all grains/grain products (bread, pizza bases and cereals) and highly processed and high CHO foods (e.g. cheese spread, ready-made sauces and pastries). Food lists using a 'traffic light system' will be provided to the participants as a reference and to enhance compliance with the diet. These lists categorise foods and drinks into: always/every day (green list), sometimes (orange list) and avoid (red list).

Minimum dietary protein intake level will be set to 1.2 g/kg – 1.7 g/kg of ideal body weight, in keeping with the Clinical Guidelines for Therapeutic Carbohydrate Restriction.[18] There will not be any upper limit intake restrictions regarding the recommended sources of fats and proteins.

A 16-week time frame for the intervention is proposed. In the first month the participants are introduced to the LC diet. Participants are invited to attend an initial 60-min group counselling session. Thereafter, participants are invited to additional one-on-one education sessions, once per week in the first four weeks and fortnightly sessions for the following 12 weeks. Sessions will take no more than 60 min and are to be held in person, or via phone call or via video conferencing if the participants prefer or if COVID-19 restrictions are in place. Participants are requested to change their diet gradually over the initial four weeks and should ideally have adjusted all their meals to the LC recommendations when attending the fourth session at the end of the first month. The counselling sessions are focused on discussion of the underlying mechanisms that drive T2DM and HF, instructions on dietary carbohydrate restriction, food selection and meal preparation, interpretation of food labels, recognition of potential side effects, establishing mindful eating techniques, difficulties in adhering to the diet and support for health behaviour change. Dietary counselling will be adapted to the personal, as well as the religious and cultural food preferences of the participants.

Participants will be asked to complete a 3-day food diary. The food diary will monitor the food intake of three consecutive days, specifically two weekdays and one weekend day (Sunday, Monday, Tuesday) at baseline, week 6 and at the end of the intervention (week 16).

Usual care group: Low fat diet

Participants randomised to the control group are supplied with the 'Living Well with Heart Failure' resource.[33] In addition, participants in the UG group are counselled to adopt a LF heart healthy diet as defined by the National Heart Foundation of Australia.[10]

Specifically, participants will be asked to (1) eat a variety of fruit and vegetables, (2) consume whole grains such as wholemeal pasta, rice and bread, (3) include lean protein-rich foods such as legumes, fish and poultry, (4) choose unflavoured LF dairy products and cheese, (5) include foods containing heart healthy fats such as nuts, olives and avocados (6) avoid processed and baked goods, sugar sweetened beverages and fast foods and (7) limit dietary sodium intake to < 2 g/day.[9]

To ensure similar intensity of intervention and to avoid bias, the UG will be coached by a research assistant who is trained to educate the participants to follow a LF heart healthy diet as defined by the National Heart Foundation of Australia.[10] Participants will be invited to attend a 60-min group counselling session at the beginning of the study (week 1). Furthermore, participants will receive a follow-up phone call by the research assistant (week 6), to provide additional information regarding heart healthy eating and to assess diet adherence and answer any questions participants may have.

All study participants will be offered the opportunity to invite a member of their family and/or household to attend the education sessions if they choose, especially in households where the participant is not usually responsible for the preparation of meals and the purchase of groceries.

Participants randomised to the UG will be offered the opportunity to complete the LC diet after completion of the study.

Data collection

Baseline collection will consist of the following demographical and biometric data: (1) age, (2) gender, (3) weight and (4) blood pressure (Table 2). In addition, the medical history of each participant will be recorded including food allergies/intolerances, current medications and relevant pathology including HbA1c. Moreover, at baseline the participants current New York Heart Association class (NYHA), is assessed. Lastly, QoL and thirst will be evaluated. Measures will be collected as described next.

New York Heart Association functional classification

The NYHA functional classification is the most frequently used system to grade functional capacity of patients with HF.[9] Depending on the extent of limitation during physical activity, patients are categorised into one of four categories.[9]

TABLE 2: Timeline for data collection.

Data collected	Baseline	Week 1	Week 2	Week 3	Week 4	Week 6	Week 8	Week 10	Week 12	Week 14	Week 16
Demographic information	X	-	-	-	-	-	-	-	-	-	-
Biometric data	X	-	-	-	-	-	-	-	-	-	X
Current medications	X	-	-	-	-	-	-	-	-	-	X
Medical history	X	-	-	-	-	-	-	-	-	-	-
Blood test results	X	-	-	-	-	-	-	-	-	-	X
Blood glucose diary	X	-	-	-	-	X	-	-	-	-	X
NYHA class	X	-	-	-	-	-	-	-	-	-	X
Thirst distress scale	X	-	-	-	-	-	-	-	-	-	X
KCCQ-12	X	-	-	-	-	-	-	-	-	-	X
3-day food diary	X	-	-	-	-	X	-	-	-	-	X
Food frequency	LC	-	-	-	-	LC	-	-	-	-	LC
Nutritional counselling sessions	-	X (GS)	LC	LC	LC	-	LC	-	LC	-	-
Follow-up phone call	-	-	-	-	-	X	-	-	-	-	-
ED presentations	-	-	-	-	-		-	-	-	-	X
Hospital admissions	-	-	-	-	-		-	-	-	-	X
Mortality	-	-	-	-	-		-	-	-	-	X

NYHA, New York Heart Association; KCCQ, Kansas City Cardiomyopathy Questionnaire; ED, emergency department; LC, low-carbohydrate group only; X, both groups; GS, group session.

As functional capacity deteriorates or improves over time, patients may move within the four categories. New York Heart Association class will be evaluated by a member of the research team at baseline and follow-up.

Thirst Distress Scale

Thirst is analysed using the eight-item validated Thirst Distress Scale for patients with HF (TDS-HF) as described by Waldréus et al.[34] This scale has been found to be valid and reliable for the assessment of thirst distress in HF patients and is used internationally.[34]

Reliability of each item, as determined by Cronbach's alpha (range 0–1), was 0.92. This reflects high internal consistency.[34]

Kansas City Cardiomyopathy Questionnaire

Quality of life is evaluated utilising Kansas City Cardiomyopathy Questionnaire (KCCQ-12). The KCCQ-12 is one of the most commonly applied and validated tools for the assessment of HF specific QoL. Initially the KCCQ was developed as a 23-item questionnaire[35]; however, a more user friendly 12-item template was developed in 2015 by Spertus and Jones.[36] In a recent prospective cohort study by Yee et al.,[37] the KCCQ-12 was not only a consistent predictor for adverse HF outcomes but also outperformed other alternatives. When compared with the full 23-item KCCQ, the KCCQ-12 did not compromise reliability and was preferred in clinical practice.[37] The established Cronbach's alpha for each domain was > 0.70. This reflects good internal consistency and reliability of the questionnaire.[35]

At the conclusion of the study all participants will be re-assessed utilising the TDS-HF and KCCQ-12 questionnaires and change to NYHA class. Any hospital admissions, emergency department presentations or mortality are recorded. Study outcomes will be measured at baseline and week 16.

Dietary intake

Participants are asked to keep a 3-day food diary using a simple food diary template, developed in consultation with a registered dietitian. The food diaries will specifically record all foods and beverages consumed over three consecutive days, on three occasions during the 16-week study period. All diaries are entered into FoodWorks 10 professional nutrition software, version 10.0. Brisbane (Xyris Pty Ltd, 2019, Brisbane, Australia) to estimate macronutrient intake and assess diet adherence.

Food frequency questionnaire

Concurrently with the 3-day food diary, participants are invited to complete a food frequency questionnaire (FFQ). As there is currently no validated FFQ specific for LC foods available, a short 12 item FFQ, using a context-specific food list has been developed by the research team. The FFQ was modified from the New Zealand Ministry of Health 2008/2009 Adult Nutrition Survey[38] and has been used in several LC studies before.[39,40] The short FFQ adds to the understanding of how often individual participants consumed CHO rich foods and beverages throughout the trial.

Glycosylated haemoglobin (HbA1c)

HbA1c levels will be collected as part of the standard practice of care (UC) at baseline and week 16.

Outcome measures

Primary outcomes

The primary outcome is a composite endpoint of changes in NYHA class, hospital admissions, thirst distress (measured by the TDS-HF), frequency of lower limb swelling, changes in weight (kg) and QoL (assessed with the KCCQ-12).[29]

Deterioration

Participants will be classified as having deteriorated if any of the following criteria are present (1) decline in NYHA by

at least one class from baseline, (2) hospitalisation for exacerbation of HF, (3) weight gain ≥ 2 kg from baseline (4) increased frequency of lower limb swelling (≥ 1 rating on a five-point Likert scale part of the KCCQ-12) from baseline, (5) increased thirst (≥ two points on the TDS-HF) from baseline, (6) reduction of QoL (≥ four points on the KCCQ-12) from baseline.

Improvement

Participants will be considered as improved if none of the above criteria are met and they demonstrate at least one of the following: (1) improvement in NYHA by one class from baseline, (2) decreased frequency of lower limb swelling (≥ 1 rating on a five-point Likert scale part of the KCCQ-12) from baseline, (3) decreased thirst (≥ two points on the TDS-HF) from baseline, (4) improved QoL (≥ four points on the KCCQ-12) from baseline and (5) weight reduction > 2 kg from baseline.

Unchanged

Participants who do not meet any of the given criteria will be classified as unchanged.

Secondary outcome

A secondary endpoint will be a 2% change in HbA1c from baseline.[41]

Safety measures

Low levels of carbohydrate intake (< 50 g per day) lead to a change in metabolism, where ketone bodies and fatty acids (as compared with glucose) become the primary energy source in the body. This state, also referred to as nutritional ketosis, is a benign process and is characterised by the presence of ketones in the blood (usually < 3 mmol/L), normal blood glucose levels, low insulin levels and an associated breakdown of adipose tissue.[18]

In contrast, the medical emergency DKA occurs most commonly in people with frank insulin deficiency such as T1DM and insulin dependent T2DM and may occur in patients taking SGLT2i. Both populations are excluded from this RCT.

Low-carbohydrate diets are considered safe; however, literature indicates that LC diets lower blood sugar levels in patients with metabolic disease and antihyperglycaemic medication frequently needs adjustment.[42,43] The authors will therefore coach participants to gradually decrease the CHO amount in their meals over the initial four weeks of the intervention to ensure more stable blood sugar levels and reduce the risk of hypoglycaemia. Participants with T2DM will be required to maintain a blood glucose diary for the duration of the study and will be asked to perform regular blood glucose measurements (at least twice per day) and anytime, if required. In addition to this, participants will be re-educated on how to recognise hypoglycaemic events and how to manage lower than normal blood sugar levels. Should participants report a hypoglycaemic event or the review of the blood glucose diary reveals consistent borderline low blood glucose levels, a researcher will liaise with the participants own health practitioner to discuss management and medication adjustment if necessary.

Low-carbohydrate diets lead to lowered plasma insulin levels and blood glucose levels, which naturally decreases SGLT2 receptor expression in the kidneys.[28] This well-known diuretic effect of the LC diet may lead to a significant decrease in blood pressure levels in study participants.[28,44] As part of the weekly education sessions, participants will be assessed for signs of orthostatic hypotension such as lightheadedness and dizziness when standing up quickly. Should participants report such symptoms, a blood pressure (BP) measurement is taken. Furthermore, participants are referred to their usual HF team for review and medication adjustment if needed.[45]

All participants will attend their regular scheduled HF specialist and other health appointments throughout the study period.

Data analysis

Descriptive statistics for continuous variables will be used to describe the mean (and standard deviation) or median (25th and 75th percentiles; interquartile range [IQR]) values from outcomes. Frequencies and chi-square will be used to describe categorical variables. Data will be analysed on an intention to treat basis with the last observation carried forward for analyses of all study participants. Missing data will be followed up with the participant after each visit. Any remaining missing data will be handled using multiple imputation. For categorical variables, independent *T*-test statistics will be used to compare independent samples. Comparisons of intervention and control group participants will use logistic regression models (with odds ratio [OR] and 95% CIs for binary variables), logistic regression for categorical variables and linear regression for approximately normally distributed continuous variables. Statistical significance will be defined as a *p*-value less than 0.05 (2-sided). All analyses will use Statistical Package for Social Sciences (SPSS) version 26 (SPSS Inc., Chicago, IL, United States).

Discussion and limitations

Nutrition and diet play a key role in the management of both HF and diabetes. Current dietary guidelines for patients with HF appear to be lacking effectiveness. Alternative diets, including LC diets should be rigorously researched in the context of HF (with and without diabetes). Low-carbohydrate eating patterns and diets consistently improve glycaemic control and have shown to effectively address dyslipidaemia in over 30 clinical trials.[13] However, limited research is available that investigates the effects of a LC diet with focus on patients with diabetes and HF.

This study aims to explore the effects of a LC diet compared with a LF diet (UG) on HF symptoms and QoL in patients with HF and T2DM or IR from a single centre quaternary metropolitan hospital in Victoria, Australia. The outcomes of this RCT will provide new insight into a dietary approach for HF with T2DM or IR and may be of interest to researchers wanting to pursue further studies in this field. In addition, the results of this RCT may be used to inform dietary guidelines for patients living with both HF and diabetes.

Some aspects of this study need to be highlighted. To assess and increase diet adherence the 3-day food diaries and FFQ have been included. All care will be taken that participants' resources are easy to use, adaptable and based on the needs of HF patients. The food lists will provide a simple and user friendly tool for study participants. However, as participants plan their meals according to the food lists, the macronutrient composition, especially CHO consumption per day may vary significantly. However, the authors believe that by selecting food items from the always/every day (green list), sometimes (orange list) and avoid (red list), the total CHO intake will be not more than 130 g/d, hence it is in line with the definition of what is considered a LC diet.[18] On the other hand, some patients may eat very low amounts of CHO throughout the study period (< 50 g/d). This may have greater therapeutic impact than a diet where an amount close to the upper limit of 130 g/d is consumed.[46]

Another potential limitation is the single centre design of the study as samples taken from multiple sites are more representative. Based on power calculations, it is believed that sample (n = 80) is large enough to give an accurate estimate of the intervention effect of this diet in RCT.

Lastly, because of recommendations in the most recent 2021 European Society of Cardiology (ECS) Guidelines for the diagnosis and management of acute and chronic HF, SGLT2i are now advised for all HF patients, regardless of diabetes status (Class I, Level A recommendation).[47] Thus, recruitment of patients with DMCM who are not currently taking SGLT2i proves to be challenging and as such this population will likely be underrepresented. This may need to be considered when interpreting the results.

Conclusion

Insulin resistance is one of the key drivers in the development and progression of DMCM. The authors' protocol describes a dietary approach targeting IR by means of therapeutic CHO restriction. This study represents a step in the evaluation of the efficacy of a LC diet intervention for patients with DMCM and may provide valuable insight into evidence-based nutrition care for this priority patient group. This study is novel and innovative as it investigates the effects of a LC diet on HF symptoms and QoL. There is paucity of research in this area. The results of this pilot RCT may be used to design larger multicentre RCTs. Future studies will be able to evaluate long-term outcomes and challenges associated with long-term LC diet adherence in patients with DMCM: a question which might not be addressed in this work.

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Competing interests

The authors declare that they have no financial or personal relationships that may have inappropriately influenced them in writing this article.

Authors' contributions

S.K.-M. was responsible for the conceptualisation, methodology, writing of original draft. B.R., A.O., C.Z. and A.D. all provided the supervision, critical feedback and helped to shape the research for this manuscript. All authors read and approved the final version of the manuscript.

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Data availability

The data sets used and analysed during this study is available from the corresponding author, S.K.-M., on reasonable request.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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