

## Protocol

# Effects of a low-carbohydrate diet in adults with type 1 diabetes: an interventional study protocol

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## ABSTRACT

**Background:** Type 1 diabetes (T1D) is an autoimmune condition characterised by pancreatic beta cell destruction and absolute insulin deficiency. The varying impact of dietary factors on blood glucose levels is well-known, yet there remains a lack of consensus surrounding the optimal dietary approaches to achieve glycaemic control in T1D. The aim of this research is to assess the efficacy of a low-carbohydrate (LC) diet in adults with T1D. We will set out to determine whether significant differences in T1D management outcomes exist between a LC diet and habitual diets higher in carbohydrate. Our primary hypothesis is that a LC diet will result in improved T1D management compared to habitual diets higher in carbohydrates.

**Methods:** This is a 28-week single arm within-participant intervention study involving a 4-week control period, a 12-week intervention period and a 12-week follow-up. We plan to recruit 20 adults (18-60 years) with T1D (duration ≥6 months) who have suboptimal glycaemic control (HbA1c >7.0%). The primary outcome is haemoglobin A1c (HbA1c) and secondary outcomes include glycaemic variability, frequency of hypoglycaemia, total daily insulin, and quality of life. This LC diet will start at 50 g of digestible carbohydrate per day and then there will be opportunity to increase or decrease within a broader range of 25-75 g/day according to individual blood glucose levels and personal preference. Participants will meet individually with the study dietitian for a total of six fortnightly sessions to receive dietary instruction, strategies, and education. Participants will continue to work with a member of their usual diabetes care team for specific advice regarding insulin management.

**Conclusions:** Current dietary management strategies for T1D appear to be lacking in effect and additional dietary therapies, including LC diets, require urgent consideration. Therefore, an interventional study investigating a patient-led LC dietary approach will be of important clinical relevance for healthcare practitioners and may help to better inform clinical practice guidelines for T1D management.

Trial Registration: <https://www.anzctr.org.au/ACTRN12621000764831.aspx>

**Keywords:** Diabetes, Glycaemic control, Low-carbohydrate diet, Diet therapy

## INTRODUCTION

Type 1 diabetes (T1D) is an autoimmune condition characterised by pancreatic beta cell destruction and absolute insulin deficiency. Individuals living with T1D must inject insulin multiple times a day to survive and can experience serious daily challenges associated with manual regulation of blood glucose levels. Modern T1D management is primarily focused on reducing risk and burden of chronic disease, including cardiovascular diseases, since the discovery of insulin in 1921 has extended the lives of individuals affected.<sup>1</sup> Achieving a haemoglobin A1c (HbA1c) of  $\leq 7.0\%$  is therefore the primary management target in diabetes as it is associated with reduced risk of developing chronic complications related to hyperglycaemia.<sup>1,2</sup> However, the high amounts of exogenous insulin commonly being used to achieve glycaemic control targets in people with T1D also has long-term health consequences, including hyperinsulinemia, which is associated with obesity, the metabolic syndrome and atherosclerosis.<sup>3,4</sup> Ultimately, adjunctive therapies that achieve glycaemic control and minimise reliance on excessive insulin are needed to improve the health and wellbeing of individuals living with T1D.

The varying impact of dietary factors on blood glucose levels is well-known, yet there remains a lack of consensus surrounding the optimal dietary approaches to achieve glycaemic control in T1D. Standard treatment involves multiple daily injections of insulin, wherein the dose of meal-time insulin is calculated based on the estimated grams or portions of carbohydrates consumed. Leading health authorities, including the national health and medical research centre (NHMRC), have traditionally recommended a high-carbohydrate (HC) diet, contributing 45-65% total energy intake (TEI), although this recommendation has been inferred from national dietary guidelines for the general population who are free from diabetes.<sup>1</sup> Data from T1D registries across 19 countries in Australasia, Europe and North America (n=324,501) reported that 84% of patients exhibited HbA1c above the desirable target range ( $>7.0\%$ ) suggesting that the current dietary advice for T1D is achieving limited impact and alternative dietary approaches should be considered.<sup>5</sup>

A separate body of evidence conducted in type 2 diabetes (T2D) shows that diets containing less than 45% TEI from carbohydrates are effective for improving glycaemic control and CVD risk. Multiple systematic reviews have demonstrated that, when compared to usual care HC diets, diets  $<45\%$  TEI from carbohydrates achieve greater reductions in HbA1c and use of diabetes medications in addition to more favourable changes in blood lipid profile, including greater increases in HDL-cholesterol and decreases in triglycerides.<sup>6-8</sup> Moreover, there is a reported dose-response effect such that HbA1c is lower with greater carbohydrate restriction.<sup>6, 7</sup> Low-carbohydrate (LC) diets are not clearly defined in the

scientific literature but in a recent systematic review (conducted by members of this team), which is the largest systematic review of all LC diets for T2D management available to-date (n=41; including all interventional study designs), LC diet interventions were defined as diets containing  $\leq 130$  g/day or 26% TEI from carbohydrate.<sup>9</sup> One 2-year trial (conducted by members of this team) compared a LC diet (14% TEI as carbohydrate) with a traditional HC diet (53% TEI as carbohydrate) in individuals with T2D and achieved greater reductions in diurnal glycaemic variability and diabetes medications alongside improvements in multiple CVD risk markers.<sup>10</sup> This cumulative evidence has led to recent updates in clinical practice guidelines globally, with acceptance of LC diets as an effective therapeutic option for T2D management by national organisations, including diabetes Australia, diabetes UK and the American diabetes association.<sup>11-13</sup>

In response to this, the interest in LC diets for T1D management has increased. Qualitative evidence has found that many patients with T1D self-restrict carbohydrates, reporting that large amounts of carbohydrates coupled with large doses of required insulin led to unpredictable blood glucose levels.<sup>14</sup> Another study reported that a lower intake of dietary carbohydrates was associated with lower HbA1c levels in outpatients with T1D.<sup>15</sup> Members of this research team recently published the first systematic review of diets  $<45\%$  TEI from carbohydrates for T1D management and nine studies were included (RCTs=2; pre-post interventions=4; retrospective case-series analyses=2; case-report=1).<sup>16</sup> Six studies reported a mean reduction in HbA1c with diets  $<45\%$  TEI from carbohydrates, with three statistically significant reductions ( $P<0.05$ ).<sup>16</sup> The LC diet arms ( $\leq 26\%$  TEI from carbohydrates) also resulted in a reduced need for exogenous insulin while maintaining (or improving) glycaemic control.<sup>16</sup> One small RCT of 10 adults reported a 33% reduction in the mean total daily insulin use (TDI) with a LC diet (50-75 g/day) compared to no change with a diet higher in carbohydrates ( $\sim 204$  g/day).<sup>17</sup> Another small RCT of 14 adults with T1D showed similar results.<sup>18</sup> No study in our review reported any statistically significant change in the negative direction for any T1D management outcome with a LC diet.<sup>16</sup> However, due to the significant heterogeneity, small sample sizes and quality of included studies, an overall effect of LC diets on T1D management could not be determined and additional research is needed.

Preliminary evidence suggests that LC diets appear safe for use in T1D and may be effective for certain subgroups of this clinical population. However, the available body of research is limited and there is still a lack of consensus regarding the efficacy of LC diets for improving T1D management. Since there are a multiplicity of lifestyle factors impacting T1D management, and with consideration that all individuals have their own personal needs and preferences, an interventional study that uses

participants as their own controls and investigates a patient-led dietary approach will be of important clinical relevance.<sup>19</sup> Therefore, a within-patient interventional study investigating a LC diet with an adaptive carbohydrate prescription (25-75 g/day) will be undertaken in adults with T1D in an outpatient setting.

The aim of this research is to assess the efficacy of a LC diet in adults with T1D. Our primary objective is to determine the effects of a LC diet (25-75 g/day) on clinical markers of T1D management including HbA1c, glycaemic variability, frequency of hypoglycaemia, TDI, and quality of life.

In adults with T1D, compared to a habitual diet that is higher in carbohydrates, a LC diet will result in: improved glycaemic control (lower HbA1c, reduced glycaemic variability, reduced frequency of hypoglycaemia), reduced TDI requirements (wherein the reduction is expected to come primarily from meal-time insulin doses) and improved quality of life and satisfaction with diabetes management

## METHODS

### *Type of study*

A 28-week single arm, within-participant controlled intervention study. This trial has been registered with the Australian New Zealand clinical trials registry (ANZCTR).

### *Sample size*

The primary outcome is HbA1c. Based on a clinically relevant difference in HbA1c of 0.7% (absolute) with a standard deviation of 1.0, to achieve 80% power with alpha <0.05, we require a sample size of n=16.<sup>17</sup> Anticipating a 20% dropout rate, we plan to recruit 20 participants into the study.

### *Participating sites*

This project will include both online (Telehealth via Zoom video conferencing) and in-person contact. Clinic visits will be conducted from a private clinic room at the Susan Wakil Health Building (SWHB) and The University of Sydney, Camperdown NSW 2006). In addition, this study provides opportunity for a member of participants' usual diabetes care team to be involved. Before entry into the study, participants will be required to nominate one member of their usual diabetes care team who is proficient in insulin management. The nominated healthcare practitioner (HCP) will be asked to confirm their ability and willingness to provide ongoing support (usual care) and medical oversight (specifically, management of insulin therapy) to their patient(s) throughout the study from their usual practice location or via Telehealth as-needed.

### *Statistical analyses*

Data will be analysed using the most up-to-date version of SPSS. Outcome results will be presented as means and standard deviations. One-way analysis of variance (ANOVA) will be used to assess the within group differences across time for each outcome.

### *Recruitment and selection of participants*

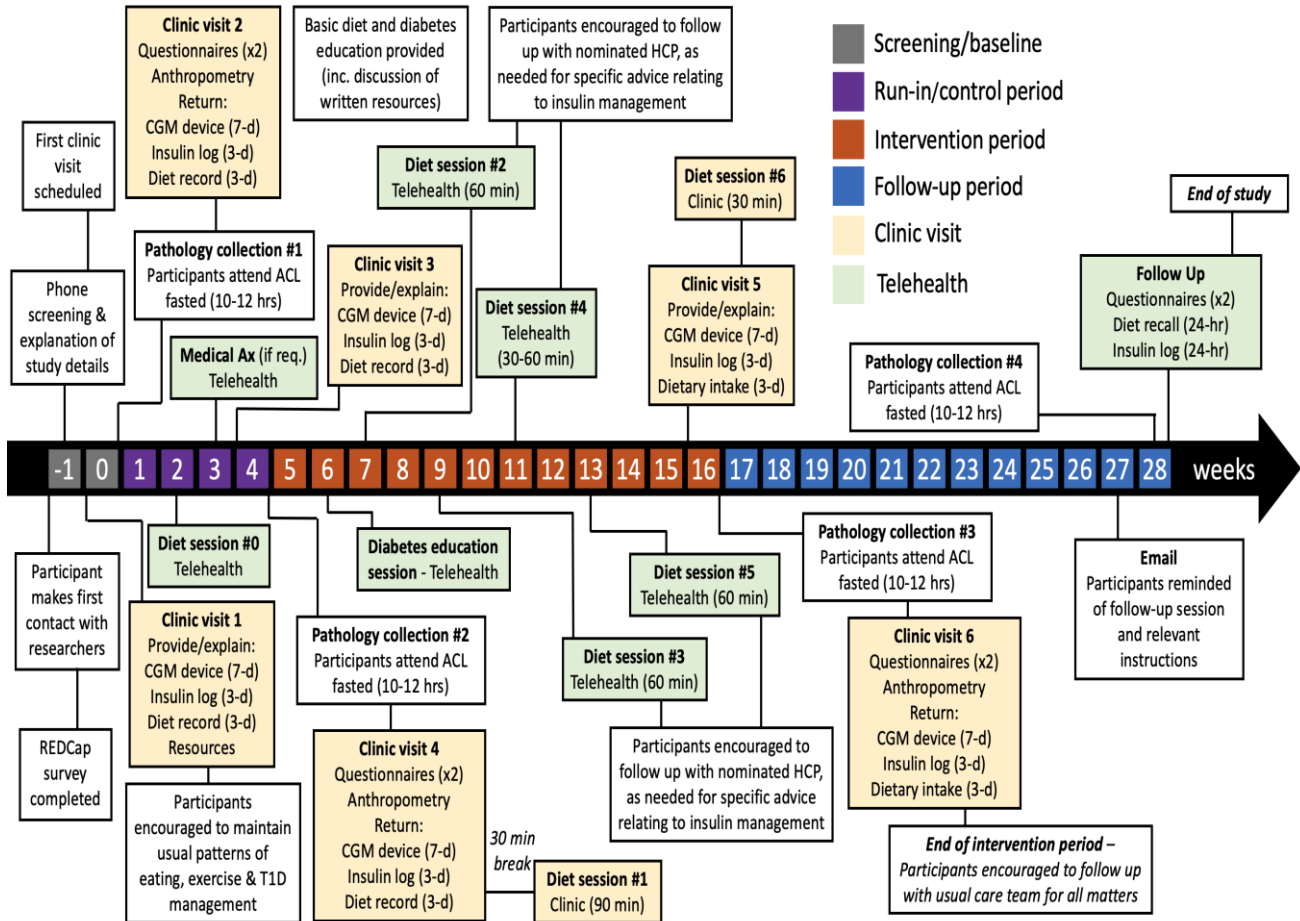
Participants will be recruited via public advertisement, including posters/flyers displayed at The University of Sydney, diabetes centres, the research site and on social media. We will also reach out to individual endocrinologists, general practitioners and diabetes educators with information on the study. Individuals wishing to take part in the study will be required to make initial contact with the researchers and complete an online survey. All potentially eligible participants will be required to provide their informed written consent by completing the survey and ticking a box to confirm they have read the Participant Information Statement (PIS) and fully understand the study details. Survey responses will be assessed in the order they are received by one investigator against the pre-specified inclusion/exclusion criteria (below). Participants will be asked to provide valid evidence to confirm their T1D diagnosis, the duration of their diabetes, and their recent HbA1c result. Ineligible participants will be excluded and provided the reason(s) for exclusion. Potentially eligible participants will receive a phone call from the researchers to clarify responses and provide additional screening information (e.g., habitual dietary intake). At this point, participants will also be asked to provide contact details i.e., of their usual GP so they can be informed of their patient's decision to be involved in the study. The first 20 eligible volunteers will be enrolled into the study (Figure 1).

### *Inclusion criteria*

To be included in this study, participants must satisfy the following inclusion criteria: adults aged 18-60 years; residing within Australia; previously diagnosed T1D (diabetes duration  $\geq 6$  months, using multiple daily injections of insulin and/or insulin pump); suboptimal glycaemic control (HbA1c >7.0%), BMI 18.5-39.9 kg/m<sup>2</sup>; habitual dietary intake contains >150 g/day of total carbohydrates; independent free-living; able to understand study requirements, speak and understand fluent English, and both physically and cognitively able to provide their informed consent, willing and able to self-monitor blood glucose levels using both finger-prick and/or continuous blood glucose monitoring devices daily, willing and able to learn and utilise dietary carbohydrate and protein counting skills, willing and able to titrate insulin dosages according to their dietary carbohydrate intake in consultation with a member of their usual diabetes care team, owns and can competently use an iOS or Android mobile device that is able to receive text messages/calls and download free mobile

applications from the App store or Google play, has access to and can competently use a computer, mobile or tablet device with internet connection for uploading data onto a secured web-based platform and for Zoom video conferencing, be willing and able to attend the clinic

rooms at the SWHB to meet with the study dietitian on up to six separate occasions throughout the study; and, be willing to visit an Australian Clinical Labs collection centre (<https://www.clinicallabs.com.au/location/>) on four separate occasions throughout the study.



**Figure 1: Overview of contact schedule for participants.**

**Exclusion criteria**

To be included in the study, participants must not satisfy any of the following exclusion criteria: HbA1c  $\leq 7.0\%$ , underweight (BMI  $< 18.5 \text{ kg/m}^2$ ) or class III obesity (BMI  $\geq 40 \text{ kg/m}^2$ ), habitual use of an automated insulin delivery system to control blood glucose levels, habitual adherence to a fixed insulin regimen such that they are not confident in titrating insulin dosages according to their dietary intake previously diagnosed hypo unawareness, non-English speaking or unable to understand English; previous medical diagnosis of cognitive impairment and/or mental illness (not including depression and anxiety), using medication to manage depression and/or anxiety and medications have been increased within the last three months, current physical impairment or disability that limits individual capacity to communicate with researchers and/or use the mobile application ‘Easy Diet Diary’, habitual dietary intake contains  $\leq 150 \text{ g/day}$  of total carbohydrates, usual dietary

intake strictly excludes animal-based protein, undertaken major change(s) to their insulin delivery method and/or glucose monitoring method within the last three months, of which they are unfamiliar, recent pregnancy or lactation (within the last six months), planning to get pregnant within the next 12 months, self-identifies as current or recent smoker (within the last 6 months), significant weight change ( $\pm 10\%$  body weight) within the last three months, previous weight loss surgery, history of malignancy (other than non-melanoma), history of thalassemia or other haemoglobinopathy, pre-existing anaemia, recent blood transfusion (within the last three months), a known family history of premature heart disease, including having a first-degree male relative or a first degree female relative who had a heart attack, stroke or was diagnosed with cardiovascular disease before the ages of 55 or 65, respectively, previously diagnosed familial hypercholesterolaemia, previously diagnosed gastrointestinal disease (not including stable treated inflammatory bowel disease or irritable bowel

syndrome), liver disease (not including fatty liver), chronic kidney disease (eGFR<60), respiratory disease (not including stable treated asthma), thyroid disease (not including stable treated hyper- or hypothyroidism) or cardiovascular disease (not including hyperlipidaemia or hypertension), previously diagnosed neurological

disorder (not including low frequency migraines [ $<10$  headache days per month]), previously diagnosed with a clinical eating disorder (including anorexia nervosa, bulimia nervosa/binge eating disorder) (within the last 5 years); and, existing patient of the study dietitian, diabetes educator, physician or endocrinologist.

**Table 1: Outline of clinic visits and diet sessions throughout the study.**

Visit/session	Outline
<b>Control period</b>	
Clinic visit 1 (start of week 0)	Study schedule explained and all visits/sessions for the control and intervention periods scheduled (inc. all sessions with study dietitian and study diabetes educator)
	Medical assessment scheduled, if necessary (i.e., for patients taking any medication(s) other than insulin).
	Equipment, demonstration and instructions provided for: - Glucose monitoring device (sensor(s) and reader) (7-day monitoring), - Insulin logbook (3-day monitoring); -diet record (participants will be shown how to download and use the Easy Diet Diary mobile App to accurately record their dietary intake) (3-day monitoring); -monitoring); and, biological samples (Australian Clinical Labs request form provided, and nearest pathology collection centre to the participant identified).
	Control period educational resources discussed.
	Participants encouraged to report any adverse events throughout the study.
	Participants encouraged to maintain usual patterns of eating activity and diabetes management.
Clinic visit 2 (end of week 0)	Morning of clinic visit 2: Participants attend their nearest Australian clinical labs collection centre (fasted) to have biological samples taken. Participants instructed to have a meal and drink fluids after blood draw and before travelling.
	Data collected (pre-control outcomes); Return/upload glucose monitoring device/data -Return/upload insulin logbook, -Return/upload diet record, -Anthropometric measurements taken (weight, height, waist circumference and blood pressure); and, questionnaires completed (quality of life, physical activity and diet satisfaction).
	Participants encouraged to maintain usual patterns of eating, activity and diabetes management.
	Control period educational resources discussed.
Diet session 0 (during week 2)	Participants encouraged to maintain usual patterns of eating, activity and diabetes management.
	Control period educational resources provided.
Medical assessment (During week 3/4)	Medical assessment completed (if required).
	Medication management plan completed (copy provided to participant, their nominated healthcare practitioner and their usual general practitioner).
Clinic visit 3 (start of week 4)	Equipment, demonstration and instructions provided for: -Glucose monitoring device (sensor(s) and reader) (7-day monitoring) -Insulin logbook (3-day monitoring) -Diet record (mobile App) (3-day monitoring) -Biological samples (Australian Clinical Labs request form provided)
	Participants encouraged to maintain usual patterns of eating, activity and diabetes management.
	Morning of clinic visit 4: Participants attend their nearest Australian clinical labs collection centre (fasted) to have biological samples taken. Participants instructed to have a meal and drink fluids after blood draw and before travelling.
	Data collected (post-control/pre-intervention outcomes): -Return/upload glucose monitoring device/data, -Return/upload insulin logbook, -Return/upload diet record, -Anthropometric measurements taken (weight, height, waist circumference and blood pressure), -Questionnaires completed (quality of life, physical activity, diet satisfaction)
Clinic visit 4 (end of week 4)	Participants encouraged to have a 30-minute break.

Continued.

Visit/session	Outline
<b>Intervention period</b>	
Diet session 1 (End of week 4) Note-same day as clinic visit 4	Brief rationale for dietary intervention explained by study dietitian.
	Initial carbohydrate target set, and meal plan provided (50 g/day).
	Hardcopy diet resource book provided and partly discussed.
	Salt pouches provided and participants instructed to measure out and use 1.5 tsp daily to prevent sodium deficiency.
	Hardcopy insulin management and diabetes self-monitoring resource pack provided.
	Participants encouraged to report any adverse events throughout the study.
Diabetes education session (during week 5/6)	Participants encouraged to follow-up with their nominated healthcare professional within 7 days to discuss insulin management in more detail.
	Review time and dates of all scheduled diet sessions.
Diet session 2 (During week 7)	Insulin management and diabetes self-monitoring resources reviewed and discussed.
	Opportunity for participant to ask general questions relating to insulin management.
	Review of dietary intake (collect diet history or review mobile App tracking) and usual care blood glucose monitoring.
	Provide individualised dietary strategies for adhering to the intervention.
	Review understanding of information provided in diet session 1.
	Discuss diet resources.
Diet session 3 (During week 9)	Participants prompted to report any adverse events experienced (self-report) over previous 2 weeks (e.g., hypoglycaemia (<3.5 mmol/L), digestive issues, low energy levels, headaches, etc.)
	Participants encouraged to follow-up with their nominated healthcare professional to discuss insulin management.
	Review of dietary intake (collect diet history or review mobile App tracking) and usual care blood glucose monitoring.
	Discuss individual preferences, including any challenges or barriers to achieving the recommended carbohydrate target.
	Carb target adjustment (opportunity 1): If appropriate, negotiate an adapted carbohydrate prescription (i.e., increase or decrease within 25-75 g/day) with the primary goal of achieving pre-specified blood glucose targets (4-6 mmol/L fasting, 4-8 mmol/L 2 hours post meal).
	New meal plan provided, if applicable (25 g/day or 60 g/day sample meal plans)
Diet session 4 (During week 11)	Provide individualised dietary strategies for adhering to the intervention.
	Review understanding of information provided in diet session 2.
	Participants prompted to report any adverse events experienced (self-report) over previous 2 weeks (e.g., hypoglycaemia (<3.5 mmol/L), digestive issues, low energy levels, headaches, etc.)
	Participants encouraged to follow-up with their nominated healthcare professional to discuss insulin management.
	Review of dietary intake (collect diet history or review mobile App tracking) and usual care blood glucose monitoring.
	Provide individualised dietary strategies for adhering to the intervention.
Diet session 5 (During week 13)	Diet resources discussed.
	Data collected on any side effects experienced by participants (self-report) over previous 2 weeks (e.g., hypoglycaemia (<3.5 mmol/L), digestive issues, low energy levels, headaches etc.).
	Participants encouraged to follow-up with their nominated healthcare professional to discuss insulin management.
	Review of dietary intake (collect diet history or review mobile app tracking) and usual care blood glucose monitoring.
	Discuss individual preferences, including any challenges or barriers to achieving the recommended carbohydrate target.
	Carb target adjustment (opportunity 2): If appropriate, negotiate an adapted carbohydrate prescription (i.e., increase or decrease within 25-75 g/day) with the primary goal of achieving pre-specified blood glucose targets (4-6 mmol/L fasting, 4-8 mmol/L 2 hours post meal).
New meal plan provided, if applicable (25 g/day or 60 g/day sample meal plans)	
Provide individualised dietary strategies for adhering to the intervention.	

Continued.

Visit/session	Outline
	Review understanding of information provided in diet session 4. Participants prompted to report any adverse events experienced (self-report) over previous 2 weeks (e.g., severe hypoglycaemia, digestive issues, low energy levels, headaches, etc.) Participants encouraged to follow-up with their nominated healthcare professional to discuss insulin management.
Diet session 6 (Start of week 16)	Review of dietary intake (collect diet history or review mobile app tracking) and usual care blood glucose monitoring. Provide individualised dietary strategies for adhering to the intervention. Participants prompted to report any adverse events experienced (self-report) over previous two weeks (e.g., are like severe hypoglycaemia, digestive issues, low energy levels, headaches, etc.) Participants encouraged to follow-up with their nominated healthcare professional to discuss insulin management.
Clinic visit 5 (start of week 16) Note-same day as diet session 6	Equipment, demonstration and instructions provided for: -Glucose monitoring device (sensor(s) and reader) (7-day monitoring), -Insulin logbook (3-day monitoring), -Diet record (Easy diet diary mobile app) (3-day monitoring), -Biological samples (Australian clinical labs request form
Clinic visit 6 (end of week 16)	Morning of clinic visit 6: Participants attend their nearest Australian clinical labs collection centre (fasted) to have biological samples taken. Participants instructed to have a meal and drink fluids after blood draw and before travelling. Data collected (post-intervention outcomes): -Return/upload glucose monitoring device/data, -Return/upload insulin logbook, -Return/upload diet record, -Anthropometric measurements taken (weight, height, waist circumference and blood pressure), - Questionnaires completed (quality of life, physical activity, diet satisfaction) End of intervention period-participants thanked for being involved in study and encouraged to follow up with usual healthcare team for all matters. Provide letter with instructions for follow-up period Provide pre-paid pathology request form for follow-up HbA1c Follow-up session scheduled and participants informed they will receive an email with instructions 2 weeks prior.
Email reminder (start of week 27)	Participants reminded that they will need to visit an Australian clinical labs pathology collection centre ~3 days before their follow-up session. Brief outline for follow-up call provided.
Follow-up session (end of week 28)	Data collected (post-control/pre-intervention outcomes): -HbA1c (collected via Australian clinical labs) -Total daily insulin use (24-hour) -Diet recall (24-hour) -Questionnaires completed (quality of life, diet satisfaction) End of study-participants thanked for being involved in study and reminded to follow up with usual healthcare team for all matters.

### Control period

The schedule of events is outlined in Table 1 and Figure 1. During the first study visit (week 0), one researcher will explain the health information that needs to be collected across the following seven days (pre-control period outcome measurements). After all baseline data has been collected, the study dietitian will provide participants with instructions for the next four weeks which is to maintain usual patterns of eating, exercise and T1D management. However, participants will be required to test their blood glucose levels at least six times daily, in accordance with standard diabetes management practices, using whatever method(s) they usually use to

test glucose. The dietitian will provide instructions and written resources on blood glucose monitoring, managing hypoglycaemia and managing sick days (Table 1). There will be a diet session (diet session 0) scheduled in after two weeks and some basic diet education on carbohydrate counting and reading food labels will be provided (Table 1). During the last week of the control period, all the same outcome measurements will be repeated (post-control/pre-intervention period measurements; Table 1 and Figure 1). On the last day of the control period (end of week 4), participants will have their first diet session of the intervention period (diet session 1) with the study dietitian and the intervention period will commence.

## **Intervention period**

### *LC diet*

The dietary prescription is based on previously reported approaches shown to be safe and effective in multiple studies of LC diet interventions conducted in individuals with T2D.<sup>9</sup> This study will investigate a LC diet with an adaptive carbohydrate prescription that starts at 50 g of digestible carbohydrate per day and is then adapted (increased or decreased) within a broader range of 25-75 g/day according to individual blood glucose levels and personal preference. Participants will also be encouraged to distribute carbohydrates evenly across the day such that total carbohydrates do not exceed 20 grams at a single eating occasion. To help participants reach nutritional adequacy, they will be encouraged to consume at least one serve of protein foods (150 g portion) with each main meal and to have three main meals daily, with or without snacks. Participants will be given a food list with suggested food sources of proteins, fats and carbohydrates to assist with meal structuring. The intake of whole foods will be emphasised (e.g., vegetables, fruits, nuts, seeds, whole grains, meat, fish, eggs, yoghurt, milk, butter, unrefined fats and oils, etc.), while the intake of refined and highly processed food products (e.g., pastries, frozen meals, refined cereals, ice-cream, fruit juice, muesli bars, etc.) will be discouraged. Sample 3-day meal plans will also be provided to participants as a guide. There will be no upper limit intake restrictions on recommended sources of proteins and fats. Recommendations for alcohol intake will be a maximum of two standard drinks daily with at least three alcohol-free days each week.

Individual dietary strategies will be geared toward helping participants meet the Recommended Dietary Intakes (RDI) and adequate intakes (AI) for essential nutrients including water (<https://www.nrv.gov.au/nutrients>), except for sodium wherein the estimated requirements for all participants are expected to increase as a result of lower insulin levels with adherence to the dietary intervention.<sup>20</sup> The adjusted recommendations for sodium in this intervention will be 3000-6000 mg/day for individuals with and without hypertension to prevent sodium deficiency.<sup>21</sup> Participants will be recommended to include at least 1.5 teaspoons of iodine-rich salt daily. The recommended amount of salt will be provided to participants in pouches and they will be instructed to measure out 1.5 teaspoons daily and add to foods and drinks.

Diet sessions will follow the structure outlined in Table 1. Participants will receive dietary instruction, strategies and education, including written resources developed by the study dietitian. Dietary education will incorporate information on carbohydrates, proteins and fats, including carbohydrate and protein counting (given the need to take protein into account when calculating meal-time insulin requirements with habitual carbohydrate restriction <100 g/day).<sup>22</sup> Participants will be encouraged to use the 'Easy

diet diary' mobile application (Xyris software) throughout the study to assist with accurate carbohydrate and protein counting for calculating insulin requirements, and as a means of helping them achieve their carbohydrate prescription.

There will be opportunity to change the carbohydrate prescription after four and eight weeks. At these diet sessions, participants will discuss their dietary intake, blood glucose levels and individual preferences with the study dietitian. Together, the patient and dietitian will decide on whether to increase or decrease the carbohydrate prescription within the range of 20-75 g/day. This adaptive, patient-led approach is designed to take individual variations in dietary preferences and insulin sensitivity into account.

### *Insulin management and self-monitoring of blood glucose*

The purpose of this study is to investigate a LC dietary intervention. However, it is not possible to make major changes to the dietary management of T1D without considering the subsequent required change(s) to insulin management. As such, all participants and their nominated HCP will be provided with an information pack at the beginning of the study that contains suggested guidelines for insulin management on a LC diet. The information pack includes resources relating to general considerations for insulin management on a LC diet; blood glucose self-monitoring; managing hypoglycaemia; and managing sick days. The information will be discussed in detail during a diabetes education session with the study diabetes educator via Telehealth, which will be scheduled within the first two weeks of the intervention period (Table 1 and Figure 1). All participants will be given regular reminders to follow up with their nominated HCP for all matters relating to insulin management, including individualised advice on insulin titrations. The study dietitian, diabetes educator, physician and endocrinologist will be available throughout the duration of the study to provide support to the participants' nominated HCPs, if needed.

Participants will be required to perform usual care practice self-monitoring blood glucose readings before each meal and two hours after meals (measured using their own blood glucose monitoring device) for insulin calculations and adjustments, and to review their dietary carbohydrate prescriptions with the dietitian. Blood glucose targets will be consistent with standard practice diabetes targets and are: 4-8 mmol/L when fasting and before meals and 4-10 mmol/L two hours after starting meals

### *Self-monitoring ketones*

For safety purposes, participants will be required to self-monitor either urine or blood ketones regularly throughout the intervention period using their usual method(s) of measuring ketones. Participants will be required to measure their ketones at least twice per week, and more under certain circumstances (e.g., if feeling



unwell) as per standard of care diabetes practices. To assist participants in doing this, the required amount of ketone test strips will be provided. A resource will be provided at the beginning of the intervention period to instruct participants on how and when to monitor for ketones, what level of ketones are and are not expected, and what to do if they are experiencing unexpected changes in blood or urine ketones. The resource will help participants understand that mild, controlled ketone readings are normal and expected with the LC dietary intervention. Nutritional ketosis is typically defined as a ketone reading within the range of 0.5-3.0 mmol/L and should not be confused with diabetic ketoacidosis (DKA) that is associated with a rapid increase in ketone levels typically 10 times the level observed with nutritional ketosis.<sup>23</sup> Nevertheless, we are taking a conservative approach and advising participants to maintain ketones  $\leq 0.6$  mmol/L, as per usual standard diabetes practice.

#### *Other medications*

Participants taking other medications that might require adjustment during the intervention period, such as oral anti-glycaemics and anti-hypertensives, will be assessed by the study physician via Telehealth prior to the commencement of the intervention period, who will develop an individual medication management plan. The purpose of this plan is for the study physician to flag any potential medication adjustments with participants' usual HCP and usual GP (unless this is the same practitioner). The expected adjustments include reductions in or changes to anti-hypertensive and anti-hyperglycaemic medications.<sup>24</sup> The study physician may also recommend the participant do additional self-monitoring (e.g., measure blood pressure once daily) to help guide any medication adjustments that may be needed. It is then ultimately up to participants' usual GP to make the decision on what precise medication adjustments are required, if any, throughout the study. The participant will be asked to report any medication changes to the study dietitian at each fortnightly diet session throughout the study so they can be recorded.

#### *Physical activity*

All participants will be encouraged to maintain their usual physical activity level throughout the entire duration of the study.

#### *Outcome measurements (post-intervention)*

During the last week of the intervention period, all outcome measurements will be collected (post-intervention period outcomes). See Table 1 and Figure 1 for a detailed schedule of what outcomes will be measured and when throughout the entire study.

#### *Follow up*

The end of the intervention period will mark the end of the active education period. However, participants will be

asked to schedule one final follow-up telehealth session with the study dietitian after another 12 weeks (Figure 1). The purpose of this part of the study is to assess what dietary approach participants choose to take after the LC diet intervention, and then-what is the impact of their diet on their HbA1c, quality of life and diet satisfaction. There will be no scheduled contact with the study dietitian, physician, or diabetes educator during this period. Participants will be advised to follow up with their usual diabetes care team for all matters.

#### *Outcomes*

All primary, secondary and additional outcomes will be measured at three time-points: (1) pre-control period, (2) post-control period/pre-intervention period, and (3) post-intervention period (Table 1). The only data being collected at follow up is HbA1c, total daily insulin, dietary intake, diabetes-related quality of life and diet satisfaction (Table 1).

#### *Primary outcome*

The primary outcome was haemoglobin A1c, HbA1c (% and mmol/mol).

#### *Secondary outcomes*

The secondary outcome were as follows-Glycaemic variability (GV) markers (including standard deviation (SD) intraday and mean amplitude of glycaemic excursions (MAGE) [derived from 7-day continuous blood glucose monitoring (CGM) data using devices supplied by Medtronic Australasia], Frequency of hypoglycaemia ( $<3.5$  mmol/l with or without symptoms) [derived from 7-day CGM data], Total daily insulin (TDI) [the sum of all long-acting and rapid-acting insulin given over a 24-hour period derived from a 3-day self-report insulin log] and Quality of life [measured using the 15-item DQOL brief clinical inventory].<sup>25</sup>

#### *Additional outcomes*

The additional outcome were-Body mass index (BMI) ( $\text{kg/m}^2$ ) [height and weight measured using standard procedures by study dietitian], Waist circumference (cm) [measured at the midline point between the lowest rib and iliac crest by study dietitian], Resting blood pressure (BP) (mmHg) [measured after 5 minutes of seated rest by study dietitian], Fasting blood glucose (mmol/L)\*, Kidney function (Sodium, potassium, chloride, bicarbonate, urea, creatinine, eGFR, calcium, corrected calcium, phosphate, uric acid)\*, Liver function (Total protein, albumin, alkaline phosphatase, total bilirubin, Gamma GT, AST, ALT, globulin, magnesium, creatine kinase)\*, Lipid studies (Cholesterol, HDL/LDL, non-HDL cholesterol, triglycerides, LDL/HDL ratio, Chol/HDL ratio)\*, physical activity level [self-report using the international physical activity questionnaire].<sup>26</sup> Dietary intake (total energy, digestible carbohydrate,

dietary fibre, protein, total fat, saturated fat, monounsaturated fat, polyunsaturated fat as kJ/day and kcal/day or g/day) [derived from self-report 3-day weighed food record collected using Xyris easy diet diary and analysed using Xyris food works professional edition] and diet satisfaction (self-report using a 6-item questionnaire).<sup>27</sup>

All biological samples will be collected and analysed by a NATA-accredited laboratory (Australian clinical Labs) using standard procedures.

### **Continuation of therapy**

At the end of the study, participants will be advised to continue following up with their usual general practitioner and HCP(s) for all matters. Participants will be able to keep all the resources provided to them throughout the intervention period and may wish to continue following the dietary intervention under the support of their usual HCP(s). If, on completion of the study, participants wish to secure an appointment with the study dietitian, study diabetes educator, study physician or study endocrinologist, they will be responsible for organising this and paying any future consulting fees arising from these consultations.

### **DISCUSSION**

LC diets typically involve a reduction in dietary carbohydrates below 130 grams per day and their efficacy has been demonstrated in various clinical populations, including T2D.<sup>9</sup> Despite being the original method to treat diabetes prior to the discovery of insulin in the early 1900's, LC diets are in conflict with national dietary guidelines to follow a HC diet and interventional studies investigating their efficacy in T1D are limited.<sup>16,28</sup> However, dietary advice designed for the general population may not be appropriate for individuals living with T1D. Currently, adults with T1D have similar energy and macronutrient intakes to adults without diabetes, which are consistent with advice from national dietary guidelines to follow a HC diet (45-65% TEI from carbohydrates).<sup>29</sup> In addition, recent data from the Australasian diabetes data network shows that the average HbA1c of adults with T1D is 8.2%, which reflects very poor glycaemic control and significantly increases their risk for developing debilitating complications related to their diabetes.<sup>30</sup>

Current dietary management strategies for T1D appear to be lacking in effect and additional dietary therapies, including LC diets, require urgent consideration. Therefore, a pre-post interventional study that uses participants as their own controls and investigates a patient-led LC dietary approach will be of important clinical relevance for healthcare practitioners and may help to better inform clinical practice guidelines for T1D management.

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